

Opioids in palliative care:
safe and effective prescribing of strong
opioids for pain in palliative care of
adults

Full guideline

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This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

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Introduction

Pain is common in advanced and progressive disease. Up to two-thirds of people with cancer experience pain that needs a strong opioid. This proportion is similar or higher in many other advanced and progressive conditions.

Despite the increased availability of strong opioids, published evidence suggests that pain which results from advanced disease, especially cancer, remains under-treated.

Each year 300,000 people are diagnosed with cancer in the UK and it is estimated that there are 900,000 people living with heart failure. Others live with chronic illness such as kidney, liver and respiratory disease, and with neurodegenerative conditions. Many people with these conditions will develop pain for which a strong opioid may be needed.

The 2008 World Cancer Declaration included a target to make effective pain control more accessible. Several key documents highlight the importance of effective pain control, including 'Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance 2004), 'Control of pain in adults with cancer' (Scottish Intercollegiate Guidelines Network guideline 106), 'A strategic direction for palliative care services in Wales' (Welsh Assembly Government 2005) and 'End of life care strategy' (Department of Health 2008).

Strong opioids, especially morphine, are the principal treatments for pain related to advanced and progressive disease, and their use has increased significantly in the primary care setting. However, the pharmacokinetics of the various opioids are very different and there are marked differences in bioavailability, metabolism and response among patients. A suitable opioid must be selected for each patient and, because drug doses cannot be estimated or calculated in advance, the dose must be individually titrated. Effective and safe titration of opioids has a major impact on patient comfort. The World Health Organization has produced a pain ladder¹ for the relief of cancer pain; strong opioids are represented on the third level of the three-step ladder.

The guideline will address first-line treatment with strong opioids for patients who have been assessed as requiring pain relief at the third level of the WHO pain ladder. It will not cover second-line treatment with strong opioids where a change in strong opioid treatment is required because of inadequate pain control or significant toxicity.

A number of strong opioids are licensed in the UK. However for pain relief in palliative care a relatively small number are commonly used. This guideline has therefore looked at the following drugs: buprenorphine, diamorphine, fentanyl, morphine and oxycodone. Misinterpretations and misunderstanding have surrounded the use of strong opioids for decades (see section 3.1), and these are only slowly being resolved. Until recently, prescribing advice has been varied and sometimes conflicting. These factors, along with the wide range of formulations and preparations, have resulted in errors causing underdosing and avoidable pain, or overdosing and distressing adverse effects. Despite repeated warnings from regulatory agencies, these problems have led on occasion to patient deaths, and resulted in doctors facing the General Medical Council or court proceedings. Additional guidance, including advice on reducing dosing errors with opioid medicines, patient safety incidents arising from medication errors involving opioids

¹The World Health Organization's pain ladder is available from <http://www.who.int/cancer/palliative/painladder/en/>

and safer use of injectable medicines is available from the National Patient Safety Agency² (NPSA).

This guideline will clarify the clinical pathway and help to improve pain management and patient safety. This guideline will not cover care during the last days of life (for example, while on the Liverpool Care Pathway).

Drug recommendations

The guideline assumes that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Who this guideline is for

The target audience is non-specialist healthcare professionals initiating strong opioids for pain in adults with advanced and progressive disease. However, the guideline is likely to be of relevance to palliative care specialists as well.

² The National Patient Safety Agency: www.nrls.npsa.nhs.uk.

Patient-centred care

This guideline offers best practice advice on the care of people with advanced and progressive disease, who require strong opioids for pain control. These patients are defined as those in severe pain who may be opioid-naïve, or those whose pain has been inadequately controlled on step two of the WHO pain ladder.

Treatment and care should take into account patients' needs and preferences. People with advanced and progressive disease, who require strong opioids for pain control, should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the [Department of Health's advice on consent](#) and the [code of practice that accompanies the Mental Capacity Act](#). In Wales, healthcare professionals should follow [advice on consent from the Welsh Government](#).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

1 Recommendations

Communication

- 1.1.1** When offering pain treatment with strong opioids to a patient with advanced and progressive disease, ask them about concerns such as:
- addiction
 - tolerance
 - side effects
 - fears that treatment implies the final stages of life.
- 1.1.2** Provide verbal and written information on strong opioid treatment to patients and carers, including the following:
- when and why strong opioids are used to treat pain
 - how effective they are likely to be
 - taking strong opioids for background and breakthrough pain, addressing:
 - how, when and how often to take strong opioids
 - how long pain relief should last
 - side effects and signs of toxicity
 - safe storage
 - follow-up and further prescribing
 - information on who to contact out of hours, particularly during initiation of treatment.
- 1.1.3** Offer patients access to frequent review of pain control and side effects.

Starting strong opioids – titrating the dose

- 1.1.4** When starting treatment with strong opioids, offer patients with advanced and progressive disease regular oral sustained-release or oral immediate-release morphine (depending on patient preference), with rescue doses of oral immediate-release morphine for breakthrough pain.
- 1.1.5** For patients with no renal or hepatic comorbidities, offer a typical total daily starting dose schedule of 20–30 mg of oral morphine (for example, 10–15 mg oral sustained-release morphine twice daily), plus 5 mg oral immediate-release morphine for rescue doses during the titration phase.
- 1.1.6** Adjust the dose until a good balance exists between acceptable pain control and side effects. If this balance is not reached after a few dose adjustments, seek specialist advice. Offer patients frequent review, particularly in the titration phase.
- 1.1.7** Seek specialist advice before prescribing strong opioids for patients with moderate to severe renal or hepatic impairment.

First-line maintenance treatment

- 1.1.8** Offer oral sustained-release morphine as first-line maintenance treatment to patients with advanced and progressive disease who require strong opioids.

- 1.1.9** Do not routinely offer transdermal patch formulations as first-line maintenance treatment to patients in whom oral opioids are suitable.
- 1.1.10** If pain remains inadequately controlled despite optimising first-line maintenance treatment, review analgesic strategy and consider seeking specialist advice.

First-line treatment if oral opioids are not suitable – transdermal patches

- 1.1.11** Consider initiating transdermal patches with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed.
- 1.1.12** Use caution when calculating opioid equivalence for transdermal patches:
- A transdermal fentanyl 12 microgram patch equates to approximately 45 mg oral morphine daily.
 - A transdermal buprenorphine 20 microgram patch equates to approximately 30 mg oral morphine daily.

First-line treatment if oral opioids are not suitable – subcutaneous delivery

- 1.1.13** Consider initiating subcutaneous opioids with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are unstable, supported by specialist advice where needed.

First-line treatment for breakthrough pain in patients who can take oral opioids

- 1.1.14** Offer oral immediate-release morphine for the first-line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment.
- 1.1.15** Do not offer fast-acting fentanyl as first-line rescue medication.
- 1.1.16** If pain remains inadequately controlled despite optimising treatment, consider seeking specialist advice.

Management of constipation

- 1.1.17** Inform patients that constipation affects nearly all patients receiving strong opioid treatment.
- 1.1.18** Prescribe laxative treatment (to be taken regularly at an effective dose) for all patients initiating strong opioids.
- 1.1.19** Inform patients that treatment for constipation takes time to work and adherence is important.
- 1.1.20** Optimise laxative treatment for managing constipation before considering switching strong opioids.

Management of nausea

- 1.1.21** Advise patients that nausea may occur when starting strong opioid treatment or at dose increase, but that it is likely to be transient.

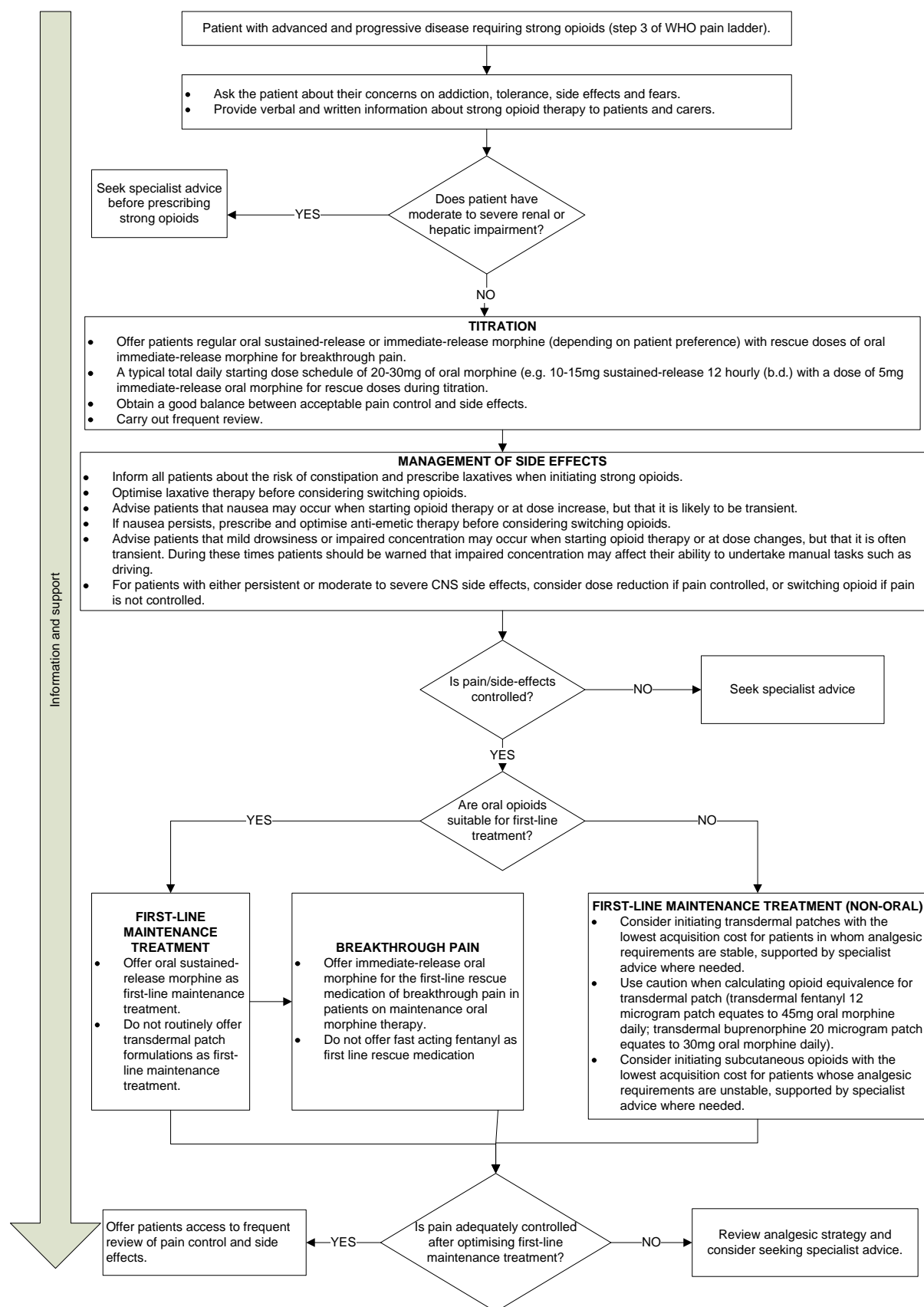
- 1.1.22** If nausea persists, prescribe and optimise anti-emetic treatment before considering switching strong opioids.

Management of drowsiness

- 1.1.23** Advise patients that mild drowsiness or impaired concentration may occur when starting strong opioid treatment or at dose increase, but that it is often transient. Warn patients that impaired concentration may affect their ability to drive³ and undertake other manual tasks.
- 1.1.24** In patients with either persistent or moderate-to-severe central nervous system side effects:
- consider dose reduction if pain is controlled **or**
 - consider switching opioids if pain is not controlled.
- 1.1.25** If side effects remain uncontrolled despite optimising treatment, consider seeking specialist advice.

³ <http://www.dft.gov.uk/dvla/medical/ataglance.aspx>

2 Care pathway



3 Evidence review and recommendations

For details of how this guideline was developed see appendix D.

3.1 Communication

Opioids are powerful medicines for pain relief and are given when weaker medications fail to provide pain relief. Several barriers to successful opioid treatment of pain have been identified. These include fear of addiction to opioids, worry about the potential for developing tolerance to treatment, concerns about side effects, reluctance to focus on pain relief rather than treating disease, fear of analgesic treatment masking symptoms of disease progression and the significance of starting opioid treatment in relation to the severity of illness. When barriers to treatment are identified and addressed, patients are more likely to take analgesia as prescribed. This may improve pain control and lessen adverse effects.

Good practice in prescribing any medicine needs an informed discussion about the potential benefits and harms of treatment before starting treatment. Ongoing monitoring of treatment should address patients' experiences and concerns about efficacy and side effects and should include discussion about how treatment might improve or impair quality of life.

3.1.1 Review question

What information do patients with advanced and progressive disease who require strong opioids, or their carers, need to:

- consent to opioid treatment, and
- monitor the effectiveness and side effects of the opioid?

3.1.2 Evidence review

This review question focused on the information that patients and carers have found to be useful or not useful, or wanted or not wanted, when considering consenting to opioid treatment and when undergoing treatment with strong opioids. Papers were included if they contained any such information reported by patients or carers. For the review protocol, inclusion/exclusion criteria, and a full list of excluded papers see appendix D. Three qualitative studies (Bender et al. 2008; Blanchard and Batten 1996; Reid et al. 2008) were identified for inclusion. All three studies examined aspects of cancer patients' information needs pertaining to pain and strong opioids. However, none of the main aims of the studies correspond to the main aims of this clinical question, and consequently the data provided by these studies are very limited. No evidence on carer information needs was identified. Table 1 lists the main characteristics of each of the included studies. GRADE was not used for this topic as it is not applicable for qualitative studies. All studies were appraised according to the NICE technical manual (2009), (see appendix E for full evidence tables).

Bender et al. (2008) conducted semi-structured interviews of 18 patients with breast cancer on what these patients wanted to know about pain. These patients wanted to know about all available options for pain control and how these drugs and treatments work, as well as about their expected side effects, and about the circumstances in which they are used to treat pain. Furthermore, the patients expressed a wish to know about the use and administration of analgesic medication, including when and how the medication should be taken, how often, for how long, when to expect pain relief, and the expected duration of the relief. Concerns about addiction and tolerance were common, particularly with respect to the use of opioids. Fear of unpleasant or unmanageable side effects prompted many to avoid or discontinue pain medication.

Blanchard and Batten (1996) interviewed 47 patients with terminal cancer, 31 of whom were either currently taking or had previously taken morphine. For 17 of the 31 patients taking or having previously taken morphine who contributed responses to the relevant (in this context) question, the most common questions or concerns related to addiction, side effects, whether opioid treatment means that end of life is near, and alcohol consumption while receiving opioid treatment. For 7 out of the 16 patients not on morphine who responded to the relevant (in this context) question, the main questions or concerns about potential morphine treatment also related to whether opioid treatment signals that end of life is near, whether morphine is a poison, and the likely side effects.

Reid et al. (2008) interviewed 18 patients with cancer who had been approached to take part in a pain management trial. These interviews showed that the patients preferred unhurried consultations in which pain was seen as important, although some of the patients did not expect their pain to be addressed during oncology clinics because of the perception that the staff already had high workloads. The interviews also showed that the manner in which the professionals communicated about opioids was important. Participants felt more able to accept inclusion in the pain management trial when they were told that opioids were being started at a 'low dose' and opioids could be discontinued if side effects developed. The patients also appreciated professionals who spoke about opioids with knowledge and confidence but were sometimes suspicious about the idea of 'choice' ('They actually don't say, "Mr Smith, would you like to take the morphine?" They always say, "it's your choice". If it is my choice, what are they not telling me?'). Half of the participants mentioned trust in the professional as an important factor in their decision to take opioids. For some of the patients, trusting the professional meant that it allowed them to make their own decision, whereas for others, trust meant that they could allow the professional to make the decision on their behalf.

Table 1 Summary of included studies for information needs of patients with advanced and progressive disease who require strong opioids for pain, or their carers

Author (year)	Study design	Population (N, inclusion criteria)	Aim and method
Bender et al. (2008)	Qualitative study	N = 18 patients with pain from breast cancer or its treatment, ≥ 18 years old, and who were able to understand spoken and written English	Semi-structured interviews examining what the patients wanted to know about pain
Blanchard and Batten (1996)	Qualitative study	N = 47 patients with terminal cancer	Interviews examining cancer patients' knowledge of morphine
Reid et al. (2008)	Qualitative study	N = 18 patients recruited from a pain management trial that took place in a UK oncology centre. All patients who both entered and declined participation in the trial were approached to request an interview	Interviews examining the factors influencing the decision to accept or reject morphine when first offered to patients with cancer

See appendix E for the evidence tables in full.

3.1.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

3.1.3.1 *Patients worry about addiction, tolerance and side effects and that opioid treatment signals that the end of life is near (three studies; VERY LOW QUALITY).*

3.1.4 Health economic modelling

This topic did not lend itself to health economic evaluation because there is no comparative analysis of cost and outcomes.

The cost difference between different interventions (different information for the patient) is likely to be minimum, so this question is considered to be of low priority for economic analysis. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.1.5 Evidence to recommendations

The aim of this topic was to determine what information patients and carers need to consent to opioid treatment and monitor the effectiveness and side effects of opioid treatment.

The primary outcome of interest was the information needs reported by patients and carers both when considering treatment and when undergoing treatment with strong opioids. No evidence was found on carers' information needs.

Evidence was found relating to patients' information needs but this was limited and of very low quality. The GDG noted that the main aims of the studies appraised did not correspond with the main aims of this clinical question. They also noted that one of the studies was from 1996 and may therefore not reflect current practice. It was also unclear if these qualitative studies had reached data saturation. Despite these limitations, the GDG agreed that the data provided by these studies would still be helpful in forming recommendations.

The available evidence reported patient concerns about the use of opioids. The GDG considered that this was an important outcome because patient concerns can have a significant impact on whether or not a patient actually takes the opioid that has been prescribed. It therefore agreed that a recommendation should be made to explore patients' concerns when offering treatment with strong opioids.

The GDG noted that the evidence supported providing information to patients and carers and therefore agreed to recommend that patients and carers should be offered information on opioid treatment. However, the GDG also noted that there was variation between studies on what information was required and the format and method in which it was provided.

The GDG felt it was important that the recommendation specified what information should be offered to patients and carers because this can be a time of great anxiety and so extra effort needs to be made to address information needs. Therefore, based on its clinical experience, the GDG recommended a minimum level of information that should be offered. The GDG was aware that by providing this level of detailed information there was a risk that patient anxiety could increase, causing them not to take the opioid. However, the GDG felt that the recommendation to explore patients' concerns would counteract this risk.

No formal cost-effectiveness analysis was conducted for this question. The GDG considered that the recommendations it had made constituted a good standard baseline of care but it was unsure of the economic implications of making these recommendations. It therefore recommended further research to investigate this.

The GDG felt that patients often have concerns about taking opioids but that provision of support is currently variable. The GDG agreed, based on its clinical experience, that it is good clinical practice to support patients during opioid treatment by frequently reviewing pain control and side effects and providing information on who to contact out of hours.

3.1.6 Recommendations and research recommendations for communication

Recommendation 1.1.1

When offering pain treatment with strong opioids to a patient with advanced and progressive disease, ask them about concerns such as:

- addiction
- tolerance
- side effects
- fears that treatment implies the final stages of life.

Recommendation 1.1.2

Provide verbal and written information on strong opioid treatment to patients and carers, including the following:

- when and why strong opioids are used to treat pain
- how effective they are likely to be
- taking strong opioids for background and breakthrough pain, addressing:
 - how, when and how often to take strong opioids
 - how long pain relief should last
- side effects and signs of toxicity
- safe storage
- follow-up and further prescribing
- information on who to contact out of hours, particularly during initiation of treatment.

Recommendation 1.1.3

Offer patients access to frequent review of pain control and side effects.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B1

What are the most clinically effective and cost-effective methods of addressing patient and carer concerns about strong opioids, including anticipating and managing adverse effects, and engaging patients in prescribing decisions?

3.2 Introduction to first-line treatment

Morphine given orally is the oldest known opioid for treating moderate to severe pain associated with advanced and progressive disease. It is advocated in several international guidelines as a first-line strong opioid in this context (WHO pain ladder (1986); 'Morphine in cancer pain: modes of administration' (EAPC 1996, 2001); 'Control of pain in adults with cancer' (SIGN 2008). In recent years, the range of strong opioids available for clinical use, and their route of delivery, has broadened considerably. This range now includes additional oral preparations, transdermal patches, subcutaneous injections and rapidly acting transmucosal preparations.

Despite the increased availability of strong opioids, published evidence suggests that pain which results from advanced disease, especially cancer, remains under-treated. The explanation for this is complex and includes failure to assess pain and monitor symptoms; patients' and professionals' fears of opioids and their adverse effects; and difficulties accessing prescriptions and analgesia. Furthermore, the increased range of treatments may confuse some prescribers and so there is a clear need to identify the evidence base in support of strong opioids and produce guidance on their use. For the purpose of this short clinical guideline, only the following drugs commonly used in palliative care were considered: buprenorphine, diamorphine, fentanyl, morphine and oxycodone. Oral, transdermal and subcutaneous routes of administration were considered because these are the commonly used methods of administration in people requiring palliative care. Intravenous and intramuscular administration were not included.

The GDG examined three contexts in which guidance would be beneficial regarding first-line opioid use for patients with advanced and progressive disease. These contexts were:

- patients with background pain for whom oral opioid treatment is suitable (see sections 3.3 and 3.4)
- patients with background pain for whom oral opioid treatment is not suitable (see sections 3.5, 3.6 and 3.7)
- patients who need opioid treatment to control breakthrough pain after receiving opioids for background pain (see section 3.8).

3.3 Starting strong opioids – titrating the dose with immediate-release, sustained-release or transdermal patches

This section deals with initiation of strong opioids in patients who are able to take oral medication. It compares oral immediate-release preparations with oral sustained-release preparations or transdermal patches. In most patients with pain requiring strong opioids it will be necessary to titrate the starting dose to find the dose that gives the optimal balance of pain relief and side effects. In some patients with stable pain it may be possible to start with sustained-release preparations – for the comparison of sustained-release preparations (oral versus transdermal) see section 3.4.

3.3.1 Review question

Are immediate-release opioids (morphine or oxycodone) more effective than sustained-release opioids (morphine or oxycodone) or transdermal patches (fentanyl or buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?

3.3.2 Evidence review

This review question focused on the effectiveness of immediate-release (IR) morphine or IR oxycodone compared with sustained-release (SR) morphine or SR oxycodone and compared with transdermal fentanyl or buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids. Papers were included if they compared either IR morphine or IR oxycodone with SR morphine, SR oxycodone, transdermal fentanyl patch or buprenorphine patches in this patient group, in a randomised controlled trial (RCT), or if they were systematic reviews of such trials. For the review protocol, inclusion and exclusion criteria, and a full list of excluded papers, see appendix D.

Although the main focus of this question was on first-line treatment with strong opioids, some of the included studies included patients who had previously received strong opioids. In such cases, the evidence quality was downgraded for indirectness (see tables 3 and 4). When possible, meta-analyses were conducted; although the possibility of subgroup analyses was explored based on IR and SR drug (morphine or oxycodone), type of transdermal patch (fentanyl or buprenorphine) and population (cancer or non-cancer), no subgroup analyses were conducted because this was not feasible.

Immediate-release opioids compared with sustained-release opioids

Immediate-release morphine compared with sustained-release morphine

Twenty-one RCTs compared IR morphine with SR morphine, eight of which were included in abstract form (Dalton et al. 1989; Deng et al. 1997; Levy et al. 1993; MacDonald et al. 1987; Poulain et al. 1990; Ranchere et al. 1991; Walsh 1985; Xu et al. 1995) while the remainder were full-text publications (Arkinstall et al. 1989; Christrup et al. 1999; Cundiff et al. 1989; Deschamps et al. 1992; Finn et al. 1993; Gillette et al. 1997; Hanks et al. 1987; Klepstad et al. 2003; Knudsen et al. 1985; Panich and Charnvej 1993; Thirlwell et al. 1989; Ventafridda et al. 1989; Walsh et al. 1992). Table 2 lists the main characteristics of each of the included studies and the GRADE summary is shown in table 3. None of the studies found any differences in pain intensity or relief between IR and SR morphine (apart from Dalton et al. [1989], who reported that 90 mg SR morphine gave improved analgesia compared with 30 mg IR morphine) and tended to find no differences in the occurrence of side

effects or adverse events (Arkinstall et al. 1989; Christrup et al. 1999; Deschamps et al. 1992; Finn et al. 1993; Gillette et al. 1997; Levy et al. 1993; MacDonald et al. 1987; Panich and Charnvej 1993; Poulain et al. 1990; Ranchere et al. 1991; Thirlwell et al. 1989; Walsh 1985; Walsh et al. 1992) with the following exceptions: Ventafridda et al. (1989) reported that compared with IR morphine, SR morphine was associated with lower daily rates of itching, dry mouth, drowsiness, nausea, vomiting, headache, and constipation. Hanks et al. (1987) reported some differences between IR and SR morphine in terms of alertness (IR better) and sleep (SR better), but both of these differed between the groups at baseline. Dalton et al. (1989) found that 90 mg SR morphine resulted in increased toxicity compared with 30 mg IR morphine. Knudsen et al. (1985) showed some suggestion that sedation rates were higher at days 1–3 (combined) in SR morphine compared with IR morphine. And Klepstad et al. (2003) reported that patients titrated with IR morphine reported significantly more tiredness at the end of titration compared with patients titrated with SR morphine. Neither of the two studies that reported health-related quality of life found any differences between IR and SR morphine treatment (Klepstad et al. 2003; Ranchere et al. 1991).

Immediate-release oxycodone compared with sustained-release oxycodone

Four RCTs compared IR oxycodone with SR oxycodone, all of which were full-text publications (Kaplan et al. 1998; Parris et al. 1998; Salzman et al. 1999; Stambaugh et al. 2001). Table 2 lists the main characteristics of each of the included studies and the GRADE summary is shown in table 4. None of the studies found any differences in pain intensity or relief between IR and SR oxycodone and none of the studies reported individually that the oxycodone formulations differed in rates of side effects or adverse events, apart from Kaplan et al. (1998) who found that SR oxycodone was associated with fewer side effects and adverse events than IR oxycodone (including headache and those associated with the digestive system). Meta-analyses of the observed side effects in three of the four RCTs (Kaplan et al. 1998; Parris et al. 1998; Salzman et al. 1999) confirmed that no differences were evident in the rate of side effects or adverse events between IR and SR oxycodone (see also table 1 and the forest plots in appendix E). The results of the remaining RCT (Stambough et al. 2001) were not included in the meta-analysis due to its cross-over design.

Immediate-release opioids compared with transdermal patches

No RCT evidence was identified for the comparison between IR morphine or oxycodone and fentanyl or buprenorphine patches.

Table 2 Summary of included studies comparing immediate-release opioids with sustained-release opioids or with transdermal patches for first-line treatment of pain

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Arkinstall et al. (1989)	Randomised, double-blind/double-dummy, cross-over study	N = 29 patients aged ≥ 19 years with an analgesic regimen ≥ 60 mg/day of oral morphine	Sustained-release morphine v immediate-release morphine	Pain intensity, supplemental morphine, side effects, patient preference
Christrup et al. (1999)	Randomised, double-blind/double-dummy, cross-over study	N = 18 outpatients with severe cancer-related pain who were stabilised on oral morphine	Sustained-release morphine v immediate-release morphine	Pain intensity, sedation, side effects
Cundiff et al. (1989)	Randomised, double-blind/double-dummy, cross-over study	N = 23 adult patients with chronic cancer pain	Sustained-release morphine v immediate-release morphine	Pain intensity, pain frequency, rescue medication, side effects
Dalton et al. (1989)	RCT (parallel groups; abstract)	N = 68 with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain relief, side effects
Deng et al. (1997)	RCT (parallel groups; abstract)	N = 17 cancer patients with moderate-severe pain	Sustained-release morphine v immediate-release morphine	Pain relief
Deschamps et al. (1992)	Randomised, double-blind/double-dummy, cross-over study	N = 20 adult patients with pain from metastatic cancer and normal haematologic, hepatic and renal function	Sustained-release morphine v immediate-release morphine	Pain intensity, supplemental immediate-release morphine, side effects
Finn et al. (1993)	Randomised, double-blind/double-dummy, cross-over study	N = 37 adult outpatients with pain from advanced cancer requiring a stable daily dose ≥ 60 mg immediate-release morphine with a life expectancy > 1 week and < 6 months.	Sustained-release morphine v immediate-release morphine	Analgesic efficacy, breakthrough pain, side effects
Gillette et al. 1997	Randomised, double-blind/double-dummy, cross-over study	N = 35 adult patients with end-stage cancer and normal renal and hepatic function	Sustained-release morphine v immediate-release morphine	Pain intensity, adverse events, side effects

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Hanks et al. (1987)	Randomised, double-blind/double-dummy, cross-over study	N = 27 patients with advanced cancer admitted to hospital for continuing care with pain that was controlled by immediate-release morphine and who had received the same dose of morphine for ≥ 7 days	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects
Kaplan et al. (1998)	RCT (parallel groups)	N = 164 patients treated with a strong single entity opioid or 10 or more tablets per day of a fixed-dose opioid/non-opioid analgesic who were receiving a stable opioid dose and had stable coexistent disease	Sustained-release oxycodone v immediate-release oxycodone	Pain intensity, discontinuation, side effects
Klepstad et al. (2003)	RCT (parallel groups)	N = 40 adult patients with chronic cancer pain despite ongoing treatment for weak to mild pain	Sustained-release morphine v immediate-release morphine	Time to acceptable pain relief, pain intensity, side effects, health-related quality of life
Knudsen et al. (1985)	Randomised, double-blind/double-dummy, cross-over study	N = 18 patients with ≥ 7 days of well-functioning regular treatment immediate-release morphine for moderate-severe pain from metastatic/invasive cancer which was not rapidly progressing and physically and psychologically able to maintain a fixed dosage schedule and to complete questionnaires at fixed time points throughout a 2-week period	Sustained-release morphine v immediate-release morphine	Pain, sedation, side effects, patient preference
Levy et al. (1993)	RCT (parallel groups; abstract)	N = 65 adults with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects, adverse events
MacDonald et al. (1987)	Randomised, double-blind, cross-over study (abstract)	N = 28 patients with advanced cancer receiving narcotics for the treatment of stable cancer pain	Sustained-release morphine v immediate-release morphine	Pain intensity, supplementary morphine, side effects

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Panich and Charnvej.(1993)	Randomised, single-blind (assessor), cross-over study without placebo control	N = 23 cancer patients referred to pain clinic	Sustained-release morphine v immediate-release morphine	Pain intensity, sleep duration, side effects, patient preference
Parris et al. (1998)	RCT (parallel groups)	N = 111 adult cancer patients receiving 6–12 tablets or capsules a day of fixed-combination analgesics (opioid/non-opioid) for cancer-related pain with stable coexistent disease	Sustained-release oxycodone v immediate-release oxycodone	Pain intensity, discontinuation, side effects
Poulain et al. (1990)	Open-label, randomised, cross-over study (abstract)	N = 84 patients with cancer pain	Sustained-release morphine v immediate-release morphine	Patient preference, pain control, side effects
Ranchere et al. (1991)	Multicentre, randomised, double-blind/double-dummy, cross-over study (abstract)	N = 52 patients with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain, quality of life, adverse events, patient preference
Salzman et al. (1999)	RCT (parallel groups)	N = 47 adult patients with stable chronic pain not adequately controlled by prior analgesic therapy with or without opioids	Sustained-release oxycodone v immediate-release oxycodone	Stable analgesia, time to stable analgesia, pain intensity Adverse events
Stambaugh et al. (2001)	Randomised, double-blind, cross-over study	N = 40 adults with moderate or severe cancer-related pain able to take oral medication	Sustained-release oxycodone v immediate-release oxycodone	Pain relief, side effects
Thirlwell et al. (1989)	Randomised, double-blind/double-dummy, cross-over study	N = 23 adult patients requiring opal opioid therapy for cancer-related pain and mentally and physically competent to comply with therapeutic protocol	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects, supplemental morphine
Ventafridda et al. (1989)	RCT (parallel groups)	N = 70 patients with pain from advanced cancer	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects
Walsh (1985)	Randomised, double-blind/double-dummy, cross-over study (abstract)	N = 36 adults with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain, side effects

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Walsh et al. (1992)	Randomised, double-blind/double-dummy, cross-over study	N = 33 adults with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain, side effects
Xu et al. (1995)	RCT (parallel groups; abstract)	N = 262 cancer patients with moderate-severe pain	Sustained-release morphine v immediate-release morphine	Pain intensity, pain relief

Abbreviations: CI, confidence interval; RCT, randomised controlled trial; v, versus.

Table 3 GRADE profile summary comparing immediate-release morphine with sustained-release morphine for first-line treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Immediate-release morphine	Relative (95% CI)	Absolute	
Pain											
21 ^a	Randomised trials	Serious ^b	No serious inconsistency	Serious ^c	No serious imprecision	None	883 ^d	729 ^d	Not pooled. No differences reported		LOW
Side effects/adverse events											
18 ^e	Randomised trials	Serious ^d	No serious inconsistency	Serious ^c	No serious imprecision	None	693 ^d	593 ^d	Not pooled. Some differences reported within some of the studies		LOW
(Health-related) quality of life											
2 ^f	Randomised trials	Serious ^g	No serious inconsistency	Serious ^h	Serious ^g	None	71 ⁱ	67 ⁱ	Not pooled. No differences reported		VERY LOW

^aPublished as full text: Arkinstall et al. (1989); Christrup et al. (1999); Cundiff et al. (1989); Deschamps et al. (1992); Finn et al. (1993); Gillette et al. (1997); Hanks et al. (1987); Klepstad et al. (2003); Knudsen et al. (1985); Panich and Charnvej (1993); Thirlwell et al. (1989); Ventafridda et al. (1989); Walsh et al. (1992). Published as abstracts Dalton et al. (1989); Deng et al. (1997); Levy et al. (1993); MacDonald et al. (1987); Poulain et al. (1990); Ranchere et al. (1991); Walsh (1985); Xu et al. (1995).

^bN = 8 of the studies were only in abstract form and could not therefore be fully evaluated. The quality of the studies reported in full varied (e.g., unclear methods of allocation concealment and randomisation, Intention-to-treat analysis not always performed).

^cNot all first-line treatment.

^dThe majority of the included studies were of cross-over design, which means that patients were counted in both treatment groups.

^eArkinstall et al. (1989); Christrup et al. (1999); Dalton et al. (1989); Deschamps et al. (1992); Finn et al. (1993); Gillette et al. (1997); Hanks et al. (1987); Klepstad et al. (2003); Knudsen et al. (1985); Levy et al. (1993); MacDonald et al. (1987); Panich and Charnvej (1993); Poulain et al. (1990); Ranchere et al. (1991); Thirlwell et al. (1989); Ventafridda et al. (1989); Walsh et al. (1985, 1992)

^fKlepstad et al. (2003), Ranchere et al. (1991).

^gOne of the studies was in abstract form only.

^hUnclear if it was first-line treatment in all patients.

ⁱSmall N.

One of the two included studies was of cross-over design, which means that patients were counted in both treatment groups.

Abbreviations: CI, confidence interval.

Table 4 GRADE profile summary comparing immediate-release oxycodone with sustained-release oxycodone for first-line treatment of pain

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release oxycodone	Immediate-release oxycodone	Relative (95% CI)	Absolute	
Pain											
4 ^a	Randomised trials	Serious ^d	No serious inconsistency	Serious ^c	No serious imprecision	None	184 ^d	188 ^d	Not pooled. No differences reported		
Side effects/adverse events											
4 ^a	Randomised trials	Serious ^d	No serious inconsistency	Serious ^c	No serious imprecision	None	184 ^d	188 ^d	No differences reported		

^a Kaplan et al. (1998); Parris et al. (1998); Salzman et al. (1999); Stambaugh et al. (2001).

^b None of the studies reported the randomisation procedure or allocation concealment adequately.

^c Not all first-line treatment.

^d One of the included studies was of cross-over design, which means that patients were counted in both treatment groups.

^a Kaplan et al. (1998); Parris et al. (1998); Salzman et al. (1999); Stambaugh et al. (2001).

^b None of the studies reported the randomisation procedure or allocation concealment adequately.

^c Not all first-line treatment.

^d One of the included studies was of cross-over design, which means that patients were counted in both treatment groups.

Abbreviations: CI, confidence interval.

3.3.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

Immediate-release opioids compared with sustained-release opioids

3.3.3.1 *Immediate-release morphine is associated with no differences in pain relief/intensity (in 21 out of 21 studies; LOW QUALITY), no differences in rates of side effects or adverse events (in 13 out of 18 studies; LOW QUALITY) and no differences in health-related quality of life (in two out of two studies; VERY LOW QUALITY) compared with sustained-release morphine.*

3.3.3.2 *Immediate-release oxycodone is associated with no differences in pain relief/intensity (in four out of four studies; LOW QUALITY) and no differences in rates of side effects/adverse events (in four out of four studies; LOW QUALITY) compared with sustained-release oxycodone.*

Immediate-release opioids compared with transdermal patches

3.3.3.3 *No RCT evidence identified.*

3.3.4 Health economic modelling

There is no significant cost difference between immediate-release and sustained-release opioids (for example, immediate-release morphine is only £0.28 more expensive than sustained-release morphine per 100 mg). In addition, the dose-finding process will only last for a few days. After the initial optimal dose has been found, virtually all patients will start to receive sustained-release opioids.

Because the cost difference between alternative interventions is very small, this topic is considered a low priority for economic analysis.

The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.3.5 Evidence to recommendations

The aim of this topic was to determine the most effective formulation of opioid (immediate- or sustained-release) for dose titration by comparing the effectiveness of immediate-release morphine or oxycodone with sustained-release morphine or oxycodone and the effectiveness of immediate-release morphine or oxycodone with a transdermal patch formulation (either fentanyl or buprenorphine). For both of these analyses the GDG considered the outcomes of pain, opioid side effects, adverse events, percentage of patients switching opioid and health-related quality of life to be the most clinically relevant.

No RCT evidence was found for the comparison of immediate-release opioid with transdermal patch formulation and therefore no outcomes were reported.

For the comparison of immediate-release and sustained-release opioids, evidence was reported for the outcomes of pain, opioid side effects, adverse events and health-related quality of life. No evidence was found for the percentage of patients switching opioid. The overall quality of the evidence across each of these outcomes was low or very low (health-related quality of life) as assessed by GRADE.

Although not specified in the question, the GDG also considered which opioid is more effective in the initial titration phase and in the subsequent maintenance phase. The evidence was of low quality and difficult to interpret, however the GDG concluded

that an immediate-release opioid and a sustained-release opioid had equivalent efficacy in both the titration and maintenance phases.

No formal cost-effectiveness analysis was conducted for this question. The GDG noted that an immediate-release opioid may be more costly because it has to be administered every 4 hours. The GDG also agreed the cost may vary depending upon setting (for example, a patient self-administering, or visiting their GP). However, the GDG concluded that the overall cost impact may not be significant because an immediate-release opioid would only be administered over a short time period.

From the available evidence, the GDG was unable to recommend a particular formulation of opioid because both immediate- and sustained-release formulations showed equivalence for all the reported outcomes. The GDG agreed that offering patients a choice of immediate- or sustained-release formulations would be likely to improve adherence because patients would be able to choose the formulation that was most acceptable to them. Based on their clinical experience, the GDG also agreed to recommend a rescue dose of immediate-release opioid when required, to minimise pain in the titration phase and hopefully improve patients' quality of life.

Because no evidence was identified in the literature to compare immediate-release opioid and transdermal patches, the GDG was unable to make a recommendation on the use of transdermal patches as a first-line treatment.

The GDG noted that specific dosing guidance would be helpful to reduce the potential harms of inappropriate doses of opioids being used by inexperienced practitioners. The GDG therefore recommended, based on its clinical experience and manufacturers' guidelines, safe starting doses of morphine when initiating treatment. The GDG also agreed that frequent review would be needed during the titration phase to ensure a balance between pain control and side effects.

The GDG was aware of the importance of prescribing rescue medication for breakthrough pain that may occur during the titration phase. Therefore the recommendation from section 3.8 was incorporated into this recommendation.

3.3.6 Recommendations on first-line treatment – starting strong opioids

Recommendation 1.1.4

When starting treatment with strong opioids, offer patients with advanced and progressive disease regular oral sustained-release or oral immediate-release morphine (depending on patient preference), with rescue doses of oral immediate-release morphine for breakthrough pain.

Recommendation 1.1.5

For patients with no renal or hepatic comorbidities, offer a typical total daily starting dose schedule of 20–30 mg of oral morphine (for example, 10–15 mg oral sustained-release morphine twice daily), plus 5 mg oral immediate-release morphine for rescue doses during the titration phase.

Recommendation 1.1.6

Adjust the dose until a good balance exists between acceptable pain control and side effects. If this balance is not reached after a few dose adjustments, seek specialist advice. Offer patients frequent review, particularly in the titration phase.

Recommendation 1.1.7

Seek specialist advice before prescribing strong opioids for patients with moderate to severe renal or hepatic impairment.

First-line maintenance treatment

This section deals with the management of background pain that requires the regular prescription of a strong opioid.

3.3.7 Review question

Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl or buprenorphine) as first-line maintenance treatment for pain in patients with advanced and progressive disease who require strong opioids?

3.3.8 Evidence review

This review question focused on the effectiveness of sustained-release (SR) morphine compared with SR oxycodone, transdermal fentanyl or buprenorphine patches, as first-line maintenance treatment for pain in patients with advanced and progressive disease who require strong opioids. Papers were included if they compared SR morphine with SR oxycodone, transdermal fentanyl patch or buprenorphine patch in this patient group, in an RCT, or if they were systematic reviews of such trials. Table 5 lists the main characteristics of each of the included studies. For the review protocol, inclusion and exclusion criteria, and a full list of excluded papers, see appendix D.

Although the main focus of this question is on first-line maintenance treatment with strong opioids, some of the included studies were not in strong-opioid-naïve patients. In such cases, the evidence quality was downgraded for indirectness (see tables 6–8). If feasible, meta-analyses with possible subgroup analysis based on the population (cancer or non-cancer) were anticipated, but the body of evidence consisted of five studies, four of which contained pooled analyses (three of these studies were systematic reviews). Therefore no further pooled analyses were performed.

Sustained-release morphine compared with sustained-release oxycodone

Bekkering et al. (2011) conducted a systematic review with network meta-analysis of RCTs on patients with chronic pain from cancer or non-cancer conditions and found that pain did not differ between the treatments regardless of treatment duration (1 day to 1 week, 1 week to 1 month, over 1 month) and when the analyses were limited to the studies on cancer pain. However, in patients with non-cancer pain, SR morphine was significantly more effective than SR oxycodone. In the studies on cancer pain, treatment discontinuation (for any reason, because of lack of efficacy, or because of adverse events) did not differ between the treatments. In a systematic review without meta-analysis, Caraceni et al. (2011) reported that a cross-over trial comparing SR morphine with SR oxycodone found no difference in pain between the treatments. However, SR morphine was associated with more nausea and vomiting. In a set of meta-analyses of four RCTs (one of which compared SR oxycodone with SR hydromorphone), Reid et al. (2006) found no differences between the treatments in pain intensity, nausea, constipation, drowsiness (analyses excluded the hydromorphone trial), concentration difficulty, hallucinations, vomiting, agitation, dizziness, poor sleep, fatigue, itch, vivid dreams, headache and sweating. There was some suggestion that SR morphine was associated with higher rates of dry mouth compared with SR oxycodone. See GRADE table 6.

Sustained-release morphine compared with transdermal patches

Sustained-release morphine compared with transdermal fentanyl patch

Network meta-analyses conducted by Bekkering et al. (2011) on data from patients with chronic pain from cancer or non-cancer conditions showed that pain did not differ between the treatments when the treatment duration was 1 day to 1 week, or over 1 month, and in patients with non-cancer pain. However, with treatment duration of 1 week to 1 month and when the analyses were limited to the studies on cancer pain, SR morphine was significantly more effective than transdermal fentanyl. In the studies on cancer pain, the odds of treatment discontinuation for any reason and because of adverse events, but not because of lack of efficacy, were reduced in patients receiving transdermal fentanyl compared with those receiving SR morphine (odds ratios = 0.43 and 0.12 respectively). One further study included in the systematic review but not the network meta-analyses of Bekkering et al. (2011) found no difference in pain intensity, nausea or vomiting, urinary retention and urticaria between the treatments, although SR morphine was associated with higher rates of constipation. In a systematic review without meta-analysis, Caraceni et al. (2011) reported that a cross-over trial comparing SR morphine with transdermal fentanyl found no difference in pain between the treatments. The side-effects data from this study are included in Tassinari et al. (2008). Meta-analyses of data extracted by Tassinari et al. (2008) from three RCTs showed that of overall side effects, overall gastrointestinal side effects, nausea, constipation, overall neurological side effects, drowsiness, patient preference and hypoventilation, only constipation and patient preference were found to differ between SR morphine and transdermal fentanyl, both favouring transdermal fentanyl (odds ratios = 2.35 and 2.32 respectively). Zuurmond and Davis (2002) reported in an abstract that although pain control and the overall impression were equivalent between SR morphine and transdermal fentanyl, transdermal fentanyl was rated more convenient to use and associated with fewer side effects.

Sustained-release morphine compared with transdermal buprenorphine patch

The network meta-analyses by Bekkering et al. (2011) showed that, in patients with treatment duration of 1 week to 1 month, SR morphine was significantly more effective in reducing pain intensity compared with transdermal buprenorphine. However, with treatment duration of over 1 month and in patients with cancer pain, transdermal buprenorphine was significantly more effective than SR morphine. The odds of treatment discontinuation for any reason, but not because of lack of efficacy, were reduced in patients receiving transdermal buprenorphine compared with those receiving SR morphine (odds ratio = 0.11). Analyses of data extracted by Tassinari et al. (2008) from one RCT showed that of overall side effects, overall gastrointestinal side effects, nausea, constipation, overall neurological side effects and drowsiness, only overall gastrointestinal side effects and constipation were found to differ between SR morphine and transdermal buprenorphine, both favouring transdermal buprenorphine (odds ratios = 4.79 and 7.5 respectively). For the review protocol and inclusion and exclusion criteria, and full list of excluded papers, please see appendix D.

Table 5 Summary of included studies comparing sustained-release morphine with sustained-release oxycodone or with transdermal patches

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Bekkering et al. (2011)	Systematic review of RCTs (excluding cross-over trials) with network meta-analysis	N = 56 (10 of which were directly relevant to the present question) RCTs that evaluated the efficacy or tolerability of step III opioids in adult patients with cancer-related or non-cancer-related chronic pain. Studies had to compare an oral or transdermal step III opioid with placebo or with another step III opioid and report on ≥ 1 of the pre-specified outcomes of efficacy	Sustained-release morphine v sustained-release oxycodone; sustained-release morphine v transdermal fentanyl; sustained-release morphine v transdermal buprenorphine	Pain intensity, treatment discontinuation
Caraceni et al. (2010)	Systematic review of RCTs (including cross-over trials) without meta-analysis	N = 2 RCTs conducted in adult patients with chronic cancer pain reporting data on patient reported efficacy and/or side effects of morphine administered orally in comparison with placebo or other opioids written in English	Sustained-release morphine v sustained-release oxycodone; sustained-release morphine v transdermal fentanyl	Efficacy, side effects
Reid et al. (2006)	Systematic review of RCTs (including cross-over trials) with meta-analysis	N = 4 RCTs comparing oxycodone with an active analgesic drug in patients with cancer-related pain. All routes of drug administration and all formulations of oxycodone were considered	Sustained-release morphine v sustained-release oxycodone; sustained-release oxycodone v sustained-release hydromorphone	Pain intensity, adverse events
Tassinari et al. (2008)	Systematic review of RCTs (including cross-over trials) with meta-analysis	N = 4 phase III RCTs comparing sustained-release morphine with transdermal opiates in patients with moderate-severe cancer pain with a defined need for opiates at the time of entering the trial	Sustained-release morphine v transdermal fentanyl; sustained-release morphine v transdermal buprenorphine	Adverse effects, patient preference, trial withdrawal
Zuurmond and Davis (2002)	Pooled analysis of 2 open-label RCTs (parallel groups; abstract)	Strong opioid-naïve patients and patients transferring from weak to strong opioids. No further details reported	Sustained-release morphine v transdermal fentanyl	Pain, side effects

Abbreviations: RCT, randomised controlled trial; v, versus.

Table 6 GRADE profile summary comparing sustained-release morphine with sustained-release oxycodone for first-line maintenance treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Sustained-release oxycodone	Relative (95% CI)	Absolute	
Pain											
9 ^a	Randomised trials	Serious ^b	No serious inconsistency	Serious ^c	No serious imprecision	none	See table 5, text in section 3.4.2 and footnote a.		No differences reported in cancer patients. See also text in section 3.2.8.1		LOW
Side effects											
5 ^d	Randomised trials	Serious ^b	No serious inconsistency	Serious ^c	No serious imprecision	none	199 ^e	195 ^e	Meta-analysis of 4 trials found no differences. See also text in section 3.2.8.1		LOW

^a This is the number of direct trials from two meta-analyses (Bekkering et al., 2011; Reid et al., 2006) and one systematic review (Caraceni et al., 2011) with the following qualifications: One of the meta-analyses also included a trial comparing hydromorphone with oxycodone (Reid et al., 2006) and the other meta-analysis was a network meta-analysis with an overall total of 56 studies (Bekkering et al., 2011).

^b Some limitations in the included studies (for example, unclear methods of sequence generation and allocation concealment, no blinding, inadequate assessment of outcome data, funding from pharmaceutical companies).

^c Not all studies on population/intervention of interest.

^d This is the number of direct trials from one meta-analysis (Reid et al., 2006) and one systematic review (Caraceni et al., 2011) with the following qualification: The meta-analyses also included a trial comparing hydromorphone with oxycodone (Reid et al., 2006).

^e The majority of the included studies were of cross-over design, which means that patients were counted in both treatment groups.

^a This is the number of direct trials from two meta-analyses (Bekkering et al., 2011; Reid et al., 2006) and one systematic review (Caraceni et al., 2011) with the following qualifications: One of the meta-analyses also included a trial comparing hydromorphone with oxycodone (Reid et al., 2006) and the other meta-analysis was a network meta-analysis with an overall total of 56 studies (Bekkering et al., 2011).

^b Some limitations in the included studies (for example, unclear methods of sequence generation and allocation concealment, no blinding, inadequate assessment of outcome data, funding from pharmaceutical companies).

^c Not all studies on population/intervention of interest.

^d This is the number of direct trials from one meta-analysis (Reid et al., 2006) and one systematic review (Caraceni et al., 2011) with the following qualification: The meta-analyses also included a trial comparing hydromorphone with oxycodone (Reid et al., 2006).

^e The majority of the included studies were of cross-over design, which means that patients were counted in both treatment groups.

Abbreviations: CI, confidence interval.

Table 7 GRADE profile summary comparing sustained-release morphine with transdermal fentanyl for first-line maintenance treatment of pain

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Transdermal fentanyl	Relative (95% CI)	Absolute
Pain										
8 ^a	Randomised trials	Serious ^b	No serious inconsistency ^c	Serious ^d	No serious imprecision	None	See text in section 3.4.2 and footnote a		4/8 studies favoured morphine ^e . 4/8 studies reported no difference. See also text in section 3.2.8.1	LOW
Side effects (excluding constipation)										
6 ^f	Randomised trials	Serious ^b	No serious inconsistency ^c	Serious ^d	No serious imprecision	None	> 311 ^g	> 314 ^g	No specific differences reported	LOW
Constipation										
6 ^f	Randomised trials	Serious ^b	No serious inconsistency	Serious ^d	No serious imprecision	None	> 311 ^g	> 314 ^g	No differences reported	LOW

^a This is the number of direct trials from one pooled analysis (Zuurmond & Davis, 2002) and two systematic reviews (Bekkering et al., 2011, Caraceni et al., 2011), one of which was a network meta-analysis with an overall total of 56 studies (Bekkering et al., 2011).

^b One study reported in abstract form only. Other studies subject to different limitations (e.g., unclear methods of sequence generation and allocation concealment, no blinding, inadequate assessment of outcome data).

^c Some discrepancy between results from three individually reported studies and the network meta-analysis.

^d Not all first-line treatment.

^e This is the result from the network meta-analysis on patients with cancer pain.

^f This is the number of direct trials from one pooled analysis (Zuurmond & Davis, 2002) and two systematic reviews (Bekkering et al., 2011, Tassinari et al., 2008),

^g One of the included studies was a cross-over trial, therefore the patients were counted in both groups. One of the included papers (Zuurmond et al. 2002) did not report the number of patients.

Abbreviations: CI, confidence interval.

Table 8 GRADE profile summary comparing sustained-release morphine with transdermal buprenorphine for first-line maintenance treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Transdermal buprenorphine	Relative (95% CI)	Absolute	
Pain											
1 ^a	Randomised trials	Serious ^b	No serious inconsistency	Serious ^c	Serious ^d	none	26 ^e	26 ^e	Weighted mean difference = -16.4 (favours buprenorphine) ^f . See also text in section 3.4.2		VERY LOW
Side effects (excluding overall gastrointestinal side effects and constipation)											
1 ^a	Randomised trials	Serious ^b	No serious inconsistency	Serious ^c	Serious ^d	none	26 ^e	26 ^e	No differences reported. See also text in section 3.2.8.1		VERY LOW
Overall gastrointestinal side effects and constipation											
1 ^a	Randomised trials	Serious ^b	No serious inconsistency	Serious ^c	Serious ^d	none	26 ^e	26 ^e	Favour transdermal buprenorphine: ORs = 4.79 and 7.5 respectively		VERY LOW

^a This is the number of direct trials from two meta-analyses (Bekkering et al., 2011; Tassinari et al., 2008) with the following qualification: One of the meta-analyses was a network meta-analysis with an overall total of 56 studies.

^b Using the Jadad scoring system, Tassinari et al. (2008) graded this study 2/5.

^c Tramadol was added to the interventions in both groups. Unclear if first-line.

^d Low N.

^e This is the number of patients in the direct trial from the two meta-analyses, of which was a network meta-analysis with an overall total of 56 studies.

^f This is the result from the analysis on patients with cancer pain.

^a This is the number of direct trials from two meta-analyses (Bekkering et al., 2011; Tassinari et al., 2008) with the following qualification: One of the meta-analyses was a network meta-analysis with an overall total of 56 studies.

^b Using the Jadad scoring system, Tassinari et al. (2008) graded this study 2/5.

^c Tramadol was added to the interventions in both groups. Unclear if first-line.

^d Low N.

^e This is the number of patients in the direct trial from the two meta-analyses, of which was a network meta-analysis with an overall total of 56 studies.

^f This is the result from the analysis on patients with cancer pain.

Abbreviations: CI, confidence interval; OR, odds ratio.

3.3.9 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

Sustained-release morphine compared with sustained-release oxycodone

3.3.9.1 *Sustained-release morphine is associated with no differences in pain relief in patients with cancer pain (in nine out of nine studies; LOW QUALITY) and differences in side effect profiles (in four out of five studies; LOW QUALITY) compared with sustained-release oxycodone.*

Sustained-release morphine compared with transdermal fentanyl patch

3.3.9.2 *Sustained-release morphine is associated with either better (in four out of eight studies; LOW QUALITY) or comparable (in four out of eight studies; LOW QUALITY) pain relief in patients with cancer pain and is associated with higher odds of constipation (in six out of six studies; LOW QUALITY), but no other side effects (in four out of six studies; LOW QUALITY) compared with transdermal fentanyl.*

Sustained-release morphine compared with transdermal buprenorphine patch

3.3.9.3 *Sustained-release morphine provides worse pain relief in patients with cancer pain (weighted mean difference = -16.4) and is associated with higher odds of overall gastrointestinal side effects (odds ratio = 4.79) and constipation (odds ratio = 7.5), but no other side effects (in one out of one study; VERY LOW QUALITY) compared with transdermal buprenorphine.*

3.3.10 Health economic modelling

Background and aims

Patients with advanced and progressive disease who have tried non-opioid analgesics and opioids conventionally used in the treatment of moderate pain but these have not worked are indicated to receive strong opioids. However, there is uncertainty over the choice of strong opioids for the maintenance treatment of background pain.

The most commonly used treatment is oral sustained-release morphine, primarily because it is cheap and easy for the patients to take. However, recently, the use of transdermal patches (fentanyl and buprenorphine) has increased substantially as a first-line approach to moderate-to-severe pain. Transdermal patch treatment may be preferred over oral treatment because of better patient adherence, fewer treatment-related adverse events and the preference of the patient.

This economic evaluation aimed to assess the cost effectiveness of first-line opioid treatments in patients with advanced and progressive disease who require strong opioids. The analysis considered the perspective of the NHS.

Methods

Economic evidence review

A systematic literature review was performed to assess the current economic literature. Three relevant studies were identified: Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006). Each of these studies described the development of an economic model to assess the cost effectiveness of oral opioids. Health effects were quantified in terms of quality-adjusted life days (QALDs) and/or quality-adjusted life years (QALYs).

All of the studies were based around the same model structure. Lehmann et al. (2002) and Greiner et al. (2006) used the same basic model structure employed in the study by Neighbors et al. (2001). Of the three papers, two considered a German perspective (Lehmann et al. 2002 and Greiner et al. 2006), while the remaining study considered a US perspective (Neighbors et al. 2001).

All the studies found transdermal fentanyl to be cost effective compared with oral sustained-release morphine, with incremental cost-effectiveness ratios (ICERs) of £17,798, £14,487 and £1406 per QALY gained in the studies by Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006) respectively. In addition, Greiner et al. (2006) showed transdermal buprenorphine to be cost effective compared with oral sustained-release morphine with an ICER of £6248 per QALY gained.

All three of the studies were deemed only partially applicable to the guideline. This was mostly a result of the studies considering countries other than the UK. In some instances, there were also concerns about the applicability of the quality of life data because they were often based on assumptions by a panel of clinical experts rather than reported directly from patients. Furthermore, potentially serious limitations were identified with all of the included studies. Many of the key model parameters, such as efficacy and resource use, were estimated using the opinion of a panel of clinical experts. In addition, potential conflicts of interest were identified in all of the studies, because the analyses were sponsored by pharmaceutical companies.

De novo economic model

Because the current economic literature didn't adequately address the decision problem, a de novo economic model was developed to assess the cost effectiveness of first-line strong opioid treatments.

The results of the clinical review were used to inform the economic model. The review suggested that the proportion of patients attaining pain relief may differ between treatments, depending on the patient population and time period considered (Tassinari et al. 2008). Furthermore, the review showed that there were no statistically significant differences in the proportion of patients who discontinue as a result of a lack of efficacy. It was therefore assumed that all treatments were equally effective (in terms of pain relief).

However, the clinical review did show differences in the side-effect profiles of the drugs. Significant reductions in constipation were observed in those patients receiving transdermal treatment compared with oral sustained-release morphine (Tassinari et al. 2008). In addition, patients receiving transdermal buprenorphine patch had significantly fewer gastrointestinal side effects than patients receiving oral sustained-release morphine (Tassinari et al. 2008). However, the comparison of oral sustained-release morphine and transdermal buprenorphine patch was based on a study with low patient numbers (N = 52) and was judged to be of very low quality. Therefore, given the limitations of the evidence base for oral sustained-release morphine and transdermal buprenorphine patch, it was decided that this comparison would not be considered in the economic evaluation.

Side-effect differences were also reported for the comparison of oral sustained-release morphine and oxycodone. According to Reid et al. (2006), oxycodone was associated with a reduction in the occurrence of dry mouth. However, this aspect was not considered in the cost-effectiveness analysis because it is unlikely to have any meaningful impact on costs and benefits. Lauretti et al. (2003) reported fewer nausea events with oxycodone but this was based on a very small study population (N = 22).

Other studies in larger populations didn't show any significant differences in nausea (four out of five studies showed no statistically significant differences in side effects).

Given that oral sustained-release morphine and oral sustained-release oxycodone were equivalent in effectiveness terms, it was decided that this comparison would not need to be modelled. A decision on the most cost-effective treatment option could instead be based on the costs associated with each treatment.

Therefore, only the comparison of transdermal fentanyl patch and oral sustained-release morphine was considered in the economic model. A Markov model was developed to assess the cost effectiveness of transdermal fentanyl patch compared with oral sustained-release morphine.

Markov models involve dividing a patient's possible prognosis into a series of discrete health states. In this case, the health states were 'Receiving original opioids', 'Opioids terminated' and 'Switching'. All patients start in the 'Receiving original opioids' health state and at each weekly cycle may transit to the 'Switching' health state (following treatment discontinuation because of an adverse event) or the 'Opioids terminated' health state (following the spontaneous, non-treatment-related resolution of their pain symptoms), or they remain in the 'Receiving original opioids' health state.

Each of the health states has an associated cost and benefit tariff that patients accrue while in that state. The costs reflect the therapy that the patient is currently receiving. Thus, patients in the 'Receiving original opioids' state incur the cost of the opioids that they started with, whereas there is no cost for patients in the 'Opioids terminated' state. Patients in the 'Switching' health state incur the cost of an alternative treatment, which is calculated as the average cost of the remaining treatments under comparison. For example, patients switching from oral sustained-release morphine incur an average of the cost of oral sustained-release oxycodone, transdermal fentanyl patch and transdermal buprenorphine patch. Patients in all health states incur the cost of a monthly GP visit, reflecting the regular monitoring of patients receiving strong opioids.

Patients on active treatment also incur the cost of concomitant laxatives, which are given to prevent the commonly experienced side effect of constipation. This is calculated as an average cost of the first line oral laxatives that are typically given (as identified by the GDG).

However, it is noted that patients receiving preventative laxatives may still experience constipation. In this event, patients incur the cost of further laxative treatments consisting of strong oral laxatives or suppositories. Following advice from the GDG, 10% of patients were estimated to require an enema and thus incurred the cost of enema treatments along with the administration cost (visit by community nurse).

The transition to the 'Switching' health state has a 'one-off' cost associated with administering the new treatment and monitoring the patient. This cost includes the cost of a GP visit, a community nurse visit, advice from a medical consultant (sought by GP) and a follow-up phone call from the GP.

Costs were calculated using dose and unit cost information from the 'British national formulary' ('BNF'), resource use and cost information from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

In terms of benefits, each health state has an associated quality of life (QoL) tariff. This reflects the model's measurement of benefits in terms of QALYs, whereby the quantity and quality of life can be expressed simultaneously. Patients in the 'Receiving original opioids' and 'Switching' health states receive a QoL value associated with controlled pain. Patients in the 'Opioids terminated' health state receive a utility value associated with reduced pain. Utility decrements are also applied to reduce QoL in those patients who experience adverse events. All utility estimates were sourced from published studies (Greiner W et al. 2006; Goossens M et al. 1999; Matza L et al. 2007; Belsey J et al. 2010; Ara R and Brazier J. 2008).

The overall costs and benefits for each treatment are then estimated on the basis of the total length of time patients spend in each health state over the time horizon that has been modelled. Given that the maximum modelled time horizon was 1 year, discount rates were not considered.

Results

The base-case results of the model are presented in table 9 for the comparison of oral sustained-release morphine compared with transdermal fentanyl patch. The results show the expected costs and benefits attained per patient over various time periods (up to 1 year). It can be seen that, at a threshold of £20,000 per QALY gained, transdermal fentanyl is not cost effective compared with oral sustained-release morphine at all time points.

Table 9 Base-case total expected costs, QALYs and ICERs for oral sustained-release morphine compared with transdermal fentanyl patch

Time point	Fentanyl		Morphine		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
1 month	£90	0.0452	£54	0.0449	£35	0.0003	£107,532
2 months	£178	0.0906	£107	0.0899	£71	0.0007	£109,469
3 months	£288	0.1474	£172	0.1463	£116	0.0011	£110,096
6 months	£573	0.2957	£342	0.2936	£231	0.0021	£110,268
12 months	£1,135	0.5950	£678	0.5908	£457	0.0042	£109,636

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Sensitivity analysis

One-way sensitivity analysis showed the key drivers of the model to be the utility decrement associated with constipation, the discontinuation rate following a constipation event and the average dose used for maintenance treatment. However, the ICER remained above £20,000 per QALY gained in all scenarios modelled.

At the request of the GDG, threshold analysis was conducted on the switching cost required to attain cost effectiveness at a threshold of £20,000. The results showed that switching costs of £3,086 and £1,873 would be required when considering the base-case scenario and the scenario with an increased utility decrement (0.20) respectively. These were considerably higher than even the highest switching costs expected by the GDG members.

The results of the probabilistic sensitivity analysis showed that there was considerable variation around the mean cost-effectiveness result. However, at a threshold of £20,000 there was only an 8% probability that transdermal fentanyl patch would be cost effective compared with oral sustained-release morphine.

As with most economic evaluations, there are a number of limitations that should be acknowledged. Firstly, in clinical practice, the dose of strong opioids required for effective management of pain typically increases over time. In the model, an average maintenance dose was applied for the duration of the modelled time horizon. However, because of the relative prices of morphine and fentanyl, it is likely that including dose increases would only further improve the cost-effectiveness of morphine.

Secondly, the assumption that patients can only switch once implies that the second treatment that a patient receives is effective and well tolerated. Clearly, this may not be the case in clinical practice but the assumption was a necessary simplification. The likely influence of this assumption is somewhat difficult to ascertain but it is possible that allowing for multiple switches would improve the cost-effectiveness of transdermal fentanyl patch.

3.3.11 Evidence to recommendations

The aim of this topic was to determine the most effective first-line maintenance treatment for patients with advanced and progressive disease for whom treatment with oral opioids is suitable.

The GDG considered the outcomes of pain and opioid side effects to be the most important. Health-related quality of life was also considered an important outcome but was not reported in the evidence.

The overall evidence quality for both pain relief and rates of side effects was very low to low, as assessed by GRADE, for all outcomes considered. The GDG was aware that the low evidence grading related to design limitations, indirectness and imprecision (some studies only included low patient numbers). Despite these limitations the GDG agreed that the results from trials were generally consistent; therefore, the GDG felt confident in making a firm recommendation. In addition, the GDG felt that if more direct trial evidence was available this would be unlikely to change the direction and magnitude of results.

The GDG noted that based on the evidence, morphine is an effective and inexpensive opioid analgesic. Although the use of morphine may result in a small increase in gastrointestinal side effects compared with transdermal patches, the GDG agreed that these could be managed by adjunctive treatments. The GDG also agreed that the use of more costly preparations would need to be justified by evidence of superior efficacy or lower side-effect burden. However, studies comparing the effectiveness of fentanyl, buprenorphine and oxycodone with morphine were of poor quality and, in the opinion of the GDG, failed to demonstrate superiority over morphine. Studies suggested that the transdermal patches may be associated with fewer gastrointestinal side effects than morphine but the benefit conferred by fentanyl was not shown to be cost effective by cost-effectiveness analysis with an ICER of £107,532 per QALY gained at 1 month. The GDG noted that the evidence comparing morphine and buprenorphine consisted of only one study, which was very low quality and had low patient numbers. Because of these limitations the GDG was uncertain of the validity of the results and cost-effectiveness modelling was therefore not carried out for this comparison. The evidence showed that morphine and oxycodone have a similar side-effect profile; however, because oxycodone is more expensive, cost-effectiveness modelling was not conducted.

Consequently, the GDG decided to recommend oral sustained-release morphine as first-line maintenance treatment for patients with advanced and progressive disease

who require strong opioids. It was also agreed that transdermal patch formulations should not be used routinely as first-line maintenance treatment.

The GDG noted that sensitivity analyses carried out in the health economic model, which were used to evaluate the magnitude of effect that would need to be seen in order to make transdermal patches cost effective compared with morphine, could not identify any clinically relevant scenario in which this would be the case. The GDG did not recommend further research in this area because it felt that if more direct trial evidence was available this would be unlikely to change the direction and magnitude of results.

3.3.12 Recommendations on first-line maintenance treatment

Recommendation 1.1.8

Offer oral sustained-release morphine as first-line maintenance treatment to patients with advanced and progressive disease who require strong opioids.

Recommendation 1.1.9

Do not routinely offer transdermal patch formulations as first-line maintenance treatment to patients in whom oral opioids are suitable.

Recommendation 1.1.10

If pain remains inadequately controlled despite optimising first-line maintenance treatment, review analgesic strategy and consider seeking specialist advice.

3.4 First-line treatment if oral opioids are not suitable – transdermal patches

This section relates to patients who cannot safely swallow oral medication or have impaired absorption from the gastrointestinal tract, for example due to nausea and vomiting. The decision to use either the transdermal route or a subcutaneous infusion (see section 3.6) will depend on clinical assessment – including whether the pain is stable or unstable, the place of care (hospital or community), the resources available, and the need for co-administration of other drugs such as anti-emetics.

3.4.1 Review question

Are transdermal fentanyl patches more effective than transdermal buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral treatment is not suitable?

3.4.2 Evidence review

This review question focused on the effectiveness of transdermal fentanyl patches compared with transdermal buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral treatment is not suitable. Papers were included if they compared transdermal fentanyl patch treatment with transdermal buprenorphine patch treatment in this patient group, in an RCT, or if they were systematic reviews of such trials. Table 10 lists the main characteristics of each of the included studies. For the review protocol, inclusion and exclusion criteria, and a full list of excluded papers, see appendix D.

Although the main focus of this question is on first-line treatment with strong opioids in patients in whom oral treatment is not suitable, some of the included studies were not in strong-opioid-naïve patients and/or it was unclear whether oral treatment was suitable for the population. In such cases, the evidence quality was downgraded for indirectness (see table 11). If feasible, meta-analyses with possible subgroups analysis based on the population (cancer or non-cancer) were anticipated. However, inspection of the body of evidence revealed that meta-analysis of the results was not feasible.

The search identified two studies comparing treatment with transdermal fentanyl with transdermal buprenorphine (Sarhan and Doghem.2009; Wirz et al. 2009). However, the study by Sarhan and Doghem (2009) was only published in abstract form and, instead of random assignment to treatment, the treatment groups in Wirz et al. (2009) consisted of randomly selected patients who were already receiving the study drugs. Sarhan and Doghem (2009) found no differences in pain, side effects, complications and treatment satisfaction between the treatment groups with the exception of drowsiness and local skin complications, which were higher in the buprenorphine group. Wirz et al. (2009) appeared to find comparable rates of constipation, defecation, nausea and vomiting between the treatments, but the interpretation of the results was hampered by the absence of statistical analyses comparing only fentanyl and buprenorphine.

Table 10 Summary of included studies comparing transdermal fentanyl patch with transdermal buprenorphine patch for first-line treatment of pain in patients for whom oral opioids are not suitable

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Sarhan and Doghem (2009)	RCT (parallel groups; abstract)	N = 32 opioid-naïve patients suffering from chronic cancer pain with visual analogue scale (VAS) ≥ 7	Transdermal fentanyl patch v transdermal buprenorphine patch	Pain, side effects and complications
Wirz et al. (2009)	Prospective study with random selection of patients already receiving study medication for > 4 weeks	N = 116 patients with cancer-related pain, pure nociceptive pain, strictly ambulatory treatment, patient cooperation, and a score of 0–3 on the ECOG Performance Status scale	Transdermal fentanyl patch v transdermal buprenorphine patch	Constipation, nausea, vomiting

Abbreviations: RCT, randomised controlled trial; v, versus.

Table 11 GRADE profile summary comparing transdermal fentanyl patch with transdermal buprenorphine patch for first-line treatment of pain in patients for whom oral opioids are not suitable

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Buprenorphine patch	Fentanyl patch	Relative (95% CI)	Absolute	
Pain											
1 ^a	Randomised trials	Serious ^b	No serious inconsistency	No serious indirectness	Very serious ^c	None	16	16	No difference reported		
Side effects											
2 ^d	Randomised trials	Very serious ^e	No serious inconsistency	Serious ^f	No serious imprecision	None	77	71	Some differences reported. See also text in section 3.5.2		

^a Sarhan et al. (2009)

^b RCT published in abstract form only, so not possible to fully appraise.

^c N = 32.

^d Sarhan et al. (2009), Wirz et al. (2009)

^e Studies either published in abstract form only or using randomly selected patients already receiving treatment drugs.

^f Not all first-line treatment.

^a Sarhan et al. (2009)

^b RCT published in abstract form only, so not possible to fully appraise.

^c N = 32.

^d Sarhan et al. (2009), Wirz et al. (2009)

^e Studies either published in abstract form only or using randomly selected patients already receiving treatment drugs.

^f Not all first-line treatment.

Abbreviations: CI, confidence interval.

3.4.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

3.4.3.1 *Transdermal fentanyl is associated with no differences in pain relief (in one out of one study; VERY LOW QUALITY) and few differences in rates of side effects (in two out of two studies; VERY LOW QUALITY) compared with transdermal buprenorphine.*

3.4.4 Health economic modelling

This topic was not considered a priority for health economic evaluation because of the limited data available. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.4.5 Evidence to recommendations

The aim of this topic was to determine the most effective transdermal patch for patients with advanced and progressive disease for whom treatment with oral opioids is not suitable.

The GDG considered the outcomes of pain relief, opioid side effects and adverse events to be the most important.

For the comparison of different transdermal patches, the overall quality of the evidence for both pain relief and rates of side effects was very low, as assessed by GRADE. The GDG was also aware that of the two studies appraised for this topic, one was only published in abstract form and the other had design limitations (instead of random assignment to treatment, the treatment groups consisted of randomly selected patients who were already receiving the study drugs).

Given that the evidence that was available was limited and of low quality, the GDG did not believe it was possible to make definitive recommendations on which transdermal patch should be offered to patients if oral opioid treatment was not suitable for them. However, the GDG recognised that while most patients in this category would have complex medical needs requiring specialist advice, there needed to be flexibility for experienced primary care practitioners to offer alternative routes of administration if the analgesic requirements are stable. Therefore it recommended that transdermal patches should be considered.

The GDG considered that there might be potential additional costs from recommending specialist advice, but that there were also likely to be cost savings as a result of a reduction in inappropriate prescription of opioids. However, the GDG was uncertain of the cost implications of making this recommendation.

3.4.6 Recommendations on first-line treatment if oral opioids are not suitable – transdermal patches

Recommendation 1.1.11

Consider initiating transdermal patches with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed.

Recommendation 1.1.12

Use caution when calculating opioid equivalence for transdermal patches:

- A transdermal fentanyl 12 microgram patch equates to approximately 45 mg oral morphine daily

- A transdermal buprenorphine 20 microgram patch equates to approximately 30 mg oral morphine daily.

3.5 First-line treatment if oral opioids are not suitable – subcutaneous delivery

Where pain is unstable and opioid requirements need to be rapidly titrated a subcutaneous infusion can be used. This is not restricted to end-of-life care. Access to appropriate equipment and trained staff to administer the medication is essential.

3.5.1 Review question

Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral treatment is not suitable?

3.5.2 Evidence review

This review question focused on the effectiveness of subcutaneous morphine compared with subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral treatment is not suitable. Papers were included if they compared subcutaneous morphine with subcutaneous diamorphine or with subcutaneous oxycodone treatment in this patient group, in an RCT, or if they were systematic reviews of such trials. However, the search identified no such papers.

3.5.3 Evidence statements

No evidence was identified on the effectiveness of subcutaneous morphine compared with subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral treatment is not suitable.

3.5.4 Health economic modelling

This topic was not considered a priority for health economic evaluation because of the limited data available. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.5.5 Evidence to recommendations

The aim of this topic was to determine the most effective subcutaneous opioid for patients with advanced and progressive disease for whom treatment with oral opioids was not suitable. Unfortunately no evidence was found comparing these interventions. Despite this lack of evidence, the GDG recognised that guidance was needed on what formulation of opioid should be used when oral opioids are not suitable and patch formulations are not appropriate.

The GDG therefore agreed, based on its clinical experience, that subcutaneous opioids should be considered for patients in whom oral opioids are not suitable and whose analgesic requirements are unstable.

The GDG was uncertain of the cost implications of making this recommendation and, consequently, stated that the subcutaneous opioid with the lowest acquisition cost should be used.

3.5.6 Recommendations on first-line treatment if oral opioids are not suitable – subcutaneous delivery

Recommendation 1.1.13

Consider initiating subcutaneous opioids with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are unstable, supported by specialist advice where needed.

3.6 First-line treatment if oral opioids are not suitable – transdermal patch versus subcutaneous delivery

This topic looked at the clinical and cost effectiveness of transdermal patches versus subcutaneous opioids in patients with stable pain in whom oral opioids are not suitable.

3.6.1 Review question

Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable?

3.6.2 Evidence review

This review question focused on the effectiveness of the best transdermal patch available compared with the best subcutaneous opioid available as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable. Papers were included if they compared the best transdermal patch (as determined by the evidence in section 3.5.2) with the best subcutaneous opioid (as determined by the evidence in section 3.6.2) in this patient group, in an RCT, or if they were systematic reviews of such trials. However, given that the search identified no papers comparing the relevant subcutaneous opioids, no such analyses could be undertaken in this question.

3.6.3 Evidence statements

No evidence was identified on the effectiveness of transdermal patch treatment compared with subcutaneous opioid treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral treatment is not suitable.

3.6.4 Health economic modelling

This topic was not considered a priority for health economic evaluation because of the limited data available. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.6.5 Evidence to recommendations

The aim of this topic was to compare transdermal patches with subcutaneous opioids for patients in whom oral opioids are not suitable and whose pain is stable. Given the lack of evidence on subcutaneous opioids, it was not possible to compare the clinical or cost effectiveness of transdermal patches and subcutaneous opioids.

However, the GDG agreed that subcutaneous opioids were likely to be more expensive than transdermal patches in the home setting, because of the need for nurse visits and the acquisition cost of the syringe driver. The GDG therefore agreed that transdermal patches would be the most appropriate intervention for this group of patients. Since recommendation 1.1.11 already covers this clinical scenario, the GDG decided not to make any further recommendations.

3.7 First-line treatment for breakthrough pain in patients who can take oral opioids

Breakthrough pain can be defined as a transient exacerbation of severe pain over a background pain. These pains may be caused by actions of the patient such as movement or coughing but may fluctuate for no identifiable reason. Breakthrough pain should be distinguished from exacerbations of pain that are dose-related, such as pain occurring shortly before the next dose of analgesia is due. The treatment of breakthrough pain may require rescue doses of strong opioids.

This section only deals with people who can take oral opioids.

3.7.1 Review question

What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)?

3.7.2 Evidence review

This review question focused on the effectiveness of immediate-release (IR) morphine compared with fast-acting fentanyl or IR oxycodone as treatment for breakthrough pain in patients with advanced and progressive disease who are currently being treated with strong opioids for background pain. Papers were included if they compared IR morphine with either IR oxycodone or fast-acting fentanyl in this patient group, in an RCT, or if they were systematic reviews of such trials. Table 12 lists the main characteristics of each of the included studies. For the review protocol and inclusion and exclusion criteria, and full list of excluded papers, see appendix D.

Although it was anticipated that meta-analyses would be conducted where possible, no such analyses were performed because it was not feasible given the body of evidence. Three studies were identified that compared IR morphine with fast-acting fentanyl: one RCT (Davies et al. 2011) and two systematic reviews (Vissers et al. 2010; Zeppetella and Ribeiro 2006).

Immediate-release morphine compared with fast-acting fentanyl for breakthrough pain

Immediate-release morphine compared with fentanyl nasal spray for breakthrough pain

Davies et al. (2011) compared fentanyl pectin nasal spray (FPNS) with IR morphine sulphate capsules in patients with breakthrough cancer pain. In a per-episode analysis with clinically meaningful pain relief defined as a 2 or more point reduction in pain intensity, Davies et al. (2011) found that at 10 and 15 (but not at 5, 30, 45 and 60) minutes FPNS was associated with a 2 or more point reduction in pain intensity in a significantly higher proportion of breakthrough pain episodes than IR morphine, and at 15 and 30 (but not at 5, 10, 45 and 60) minutes FPNS was associated with pain relief of 2 or more points in a significantly higher proportion of breakthrough pain episodes than IR morphine. At 15, 30, 45 and 60 (but not 10) minutes, significantly more episodes achieved maximum total pain relief of 33% or more after FPNS compared with IR morphine. The percentage of episodes requiring rescue medication did not differ between FPNS and IR morphine, but patient satisfaction was superior for FPNS compared with IR morphine. Six FPNS and two IR morphine treatments (in eight patients) resulted in discontinuation of the study drug, and nasal tolerability did not differ between the treatments.

Vissers et al. (2010) conducted a systematic review of RCTs with a network meta-analysis that compared the efficacy of intranasal fentanyl spray (INFS), oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT) and IR morphine capsules for the treatment of breakthrough cancer pain (but only the results relevant to the questionnaire reported here). Six RCTs were included, four of which compared placebo with OTFC (Farrar et al. 1998, N = 92), INFS (Kress et al. 2009, N = 111), and FBT (Portenoy et al. 2006, N = 77; Slatkin et al. 2007, N = 86). The other two trials compared OTFC with IR morphine capsules (Coluzzi et al. 2001, N = 89 – also included in Zeppetella et al. 2009) and INFS with OTFC (Mercadante et al. 2009, N = 139). The network meta-analysis showed that statistically significantly larger pain intensity differences were associated with INFS than IR morphine at 15, 30, 45 and 60 minutes.

Immediate-release morphine compared with oral transmucosal fentanyl for breakthrough pain

In a Cochrane review (without a meta-analysis) that aimed to determine the efficacy and adverse events of opioid analgesics (given by any route) used for the management of breakthrough pain in patients with cancer, Zeppetella and Ribeiro (2006) included four RCTs, three of which are not relevant to the present question. The fourth RCT compared OTFC with IR morphine (Coluzzi et al. 2001; N = 134, of whom N = 93 were randomised) and the results of this RCT are the only results that are reported from this Cochrane review. Coluzzi et al. (2001) found that OTFC was associated with superior pain relief and pain intensity difference at 15, 30, 45 and 60 minutes, and with global performance rating compared with IR morphine. OTFC was also associated with more than a 33% change in pain intensity at 15 minutes in significantly more pain episodes than IR morphine.

Immediate-release morphine compared with immediate-release oxycodone for breakthrough pain

No evidence was identified that compared IR morphine with IR oxycodone.

.

Table 12 Summary of included studies comparing immediate-release morphine with fast-acting fentanyl or with immediate-release oxycodone for breakthrough pain

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Davies et al. (2011)	Multicentre, randomised, double-blind/double-dummy, cross-over study	N = 110 patients with a histologically confirmed diagnosis of cancer, who were receiving a fixed-schedule opioid regimen at a total daily dose \geq 60 mg/day oral morphine for background cancer-related pain, and had 1–4 episodes/day of moderate-severe breakthrough pain	Fentanyl pectin nasal spray v immediate-release morphine sulphate capsules	Pain intensity at 5, 10, 15, 30, 45 and 60 minutes, pain relief at 5, 10, 15, 30, 45 and 60 minutes after dosing. Adverse events, nasal assessments, patient satisfaction
Vissers et al. (2010)	Systematic review with network meta-analysis	N = 6 RCTs on the management of breakthrough pain that allows comparison of intranasal fentanyl spray, fentanyl buccal tablet, oral transmucosal fentanyl nitrate and immediate-release morphine in adult cancer patients suffering from breakthrough pain and treated with opioid analgesics for the management of background pain reporting pain intensity difference	Intranasal fentanyl spray, fentanyl buccal tablet, oral transmucosal fentanyl nitrate v immediate-release morphine capsules, placebo	Pain intensity difference
Zeppetella and Ribeiro (2006)	Cochrane review without meta-analysis	N = 1 multicentre, randomised, double-blind/double-dummy, cross-over study with 93 randomised patients	Oral transmucosal fentanyl citrate v immediate-release morphine capsules	Pain relief, pain intensity difference

Abbreviations: RCT, randomised controlled trial; v, versus.

Table 13 GRADE profile summary comparing fentanyl nasal spray with immediate-release morphine capsules for the treatment of breakthrough pain

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fentanyl nasal spray	Immediate-release morphine capsules	Relative (95% CI)	Absolute
Pain at 15 and 30 minutes										
2 ^a	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious ^d	None	> 110 ^a	> 100 ^a	Not pooled. Favours fentanyl nasal spray	MODERATE
Pain at 45 and 60 minutes										
2 ^a	Randomised trials	No serious limitations	Serious ^c	No serious indirectness	Serious ^d	None	> 110 ^a	> 100 ^a	Not pooled. See footnote c	LOW

^aTwo studies were included, one of which was a randomised cross-over trial with 110 patients (who are therefore counted in both treatment groups; Davies et al., 2011) and the other of which was a network meta-analysis with an overall total of six studies (none of which were direct trials; Vissers et al., 2010).

^b Small N.

^c Treatments differ in one, but not in the other study.

^a Two studies were included, one of which was a randomised cross-over trial with 110 patients (who are therefore counted in both treatment groups; Davies et al., 2011) and the other of which was a network meta-analysis with an overall total of six studies (none of which were direct trials; Vissers et al., 2010).

^b Small N.

^c Treatments differ in one, but not in the other study.

Abbreviations: CI, confidence interval.

Table 14 GRADE profile summary comparing oral transmucosal fentanyl with immediate-release morphine capsules for the treatment of breakthrough pain

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oral transmucosal fentanyl	Immediate-release morphine capsules	Relative (95% CI)	Absolute
Pain at 15, 30, 45 and 60 minutes (pain intensity difference, pain relief)										
1 ^a	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious ^b	None	93 ^c	93 ^c	Favours oral transmucosal fentanyl	LOW

^a Coluzzi et al. (2001) as reported in Zeppetella and Ribeiro (2006).

^b Small N.

^c The study was a cross-over trial so patients counted in both groups.

Abbreviations: CI, confidence interval.

3.7.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

Immediate-release morphine compared with fast-acting fentanyl for breakthrough pain

3.7.3.1 *Fentanyl nasal spray is associated with a better improvement in pain at 15 and 30 minutes (in two out of two studies; MODERATE QUALITY), but not at 45 and 60 minutes (in one out of two studies; LOW QUALITY) compared with immediate-release morphine capsules.*

3.7.3.2 *Oral transmucosal fentanyl is associated with a better improvement in pain at 15, 30, 45 and 60 minutes (in one out of one studies; LOW QUALITY) compared with immediate-release morphine capsules.*

Immediate-release morphine compared with immediate-release oxycodone for breakthrough pain

3.7.3.3 *No RCT evidence identified.*

3.7.4 Health economic modelling

This topic was considered a lower priority for health economic evaluation than the comparison of sustained-release preparations in maintenance treatment (see section 3.4.4). The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.7.5 Evidence to recommendations

The aim of this topic was to determine the most effective strong opioid treatment for breakthrough pain for those patients who are taking strong opioids for background pain, thereby improving their quality of life while avoiding adverse events or side effects. For this topic the GDG identified breakthrough and background pain, opioid side effects, adverse events, and health-related quality of life to be the most relevant outcomes.

No RCT evidence was found comparing immediate-release morphine with immediate-release oral oxycodone. However the GDG agreed, based on its clinical experience, that oxycodone and morphine have very similar efficacies and side-effect profiles when used to manage breakthrough pain. However, morphine is significantly less expensive than oxycodone. Therefore, the GDG agreed to recommend that morphine is used for the first-line management of breakthrough pain.

For the comparison of immediate-release morphine with fast-acting fentanyl, evidence was reported for intranasal fentanyl compared with immediate-release morphine and for transmucosal fentanyl compared with immediate-release morphine. This evidence related only to breakthrough cancer pain. The GDG was aware that the available literature on non-cancer related breakthrough pain is consistent with results from the cancer population and therefore the GDG agreed it was appropriate to extrapolate this evidence to the wider population. No evidence was found for sublingual and buccal fentanyl (compared with immediate-release morphine). The overall quality of the evidence across each of these interventions ranged from low to moderate as assessed by GRADE.

Pain was the only outcome reported from the available evidence. No evidence was found for opioid side effects, adverse events, health-related quality of life or the percentage of patients switching opioid. Because the patients included in these trials

were already on other opioids, it was difficult to attribute side effects to the opioids given for breakthrough pain.

Evidence reported in both systematic reviews and one RCT suggested that intranasal fentanyl was associated with superior pain relief at particular time points compared with immediate-release morphine. Although this difference was statistically significant differences were reported at only two out of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients taking morphine. The GDG did not think that these differences in pain relief from this single moderate quality trial were clinically relevant. The GDG was also aware of the relatively small population size in each of the included studies.

No formal cost-effectiveness analysis was conducted for this question and a systematic review of the economic literature yielded no relevant data. The cost of treating an average breakthrough event was calculated, as shown in table 15. For the purpose of the costing exercise, it is assumed that the dose of the immediate-release preparations is equal to one-sixth of the regular daily dose. The GDG noted that fast-acting fentanyls (especially those which also require a spray canister) are considerably more expensive than immediate-release morphine.

Table 15 Costs of breakthrough pain medication

Therapy	Regular dose	Breakthrough dose ^a	Average price per breakthrough event
Morphine	60 mg	10 mg	£0.09
Oxycodone	30 mg	5 mg	£0.20
Fentanyl	25 µg/h ^b		
Intranasal ^c		100 µg	£4.88
Sublingual		100 µg	£4.99
Buccal		100 µg ^d	£4.99
Buccal		200 µg ^e	£5.85

^a Typically one-sixth of regular daily dose.

^b Patch dose. ^c Average of Instanyl (100 µg) and PecFent (100 µg).

^d Initial dose of Effentora (100 µg).

^e Initial doses of Actiq (200 µg).

The GDG was satisfied that there was limited evidence to suggest that fentanyl is more clinically effective than immediate-release morphine (and immediate-release oxycodone) for the management of breakthrough pain. However, it felt the cost impact of recommending fentanyl over immediate-release morphine or oxycodone would be considerable and therefore could not be justified. Therefore, the GDG agreed to recommend that fast-acting fentanyls are not offered.

3.7.6 Recommendations on breakthrough pain

Recommendation 1.1.14

Offer oral immediate-release morphine for the first-line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment.

Recommendation 1.1.15

Do not offer fast-acting fentanyl as first-line rescue medication.

Recommendation 1.1.16

If pain remains inadequately controlled despite optimising treatment, consider seeking specialist advice.

3.8 Management of constipation

Constipation is common in patients receiving palliative care for advanced and progressive disease. It may be associated with other factors such as flatulence, bloating, or a sensation of incomplete evacuation. Opioids can cause constipation by different mechanisms: they decrease muscular propulsive intestinal activity, increase non-propulsive activity and enhance the absorption of fluid and electrolytes from the bowel lumen. Although general principles for avoiding constipation should be followed, patients taking opioids will often need pharmacological intervention in the form of one or several laxatives. They may need to be admitted to hospital or hospice because further investigation and more interventional management (for instance, regular enemas) often cannot be undertaken at home. Complications of constipation can include pain, overflow diarrhoea, bowel obstruction and urinary retention.

Some opioids are thought to be more constipating than others (see section 3.4.2). The GDG wanted to investigate the evidence on whether laxative treatment or switching the type of opioid medication would be a more effective intervention in reducing constipation for patients with troublesome constipation on opioids.

The GDG felt that adherence to laxative treatment was important. It was felt that a significant proportion of patients in primary and secondary care did not take laxatives regularly, if at all.

3.8.1 Review question

Is laxative treatment more effective with or without opioid switching in reducing constipation in patients with advanced and progressive disease who are taking strong opioids and experience constipation as a side effect?

3.8.2 Evidence review

This review question focused on the effectiveness of laxatives for the treatment of constipation resulting from strong opioids taken for pain by patients with advanced and progressive disease. Papers were included if they compared laxative treatment with or without an associated switch in opioid in patients experiencing constipation from strong opioid treatment, in RCTs, or if they were systematic reviews of such trials:

However, the search identified no such papers.

3.8.3 Evidence statements

3.8.3.1 *No evidence was identified on the effectiveness of laxative treatment with or without opioid switching in patients experiencing constipation as a side effect of strong opioid treatment.*

3.8.4 Health economic modelling

This topic was not considered a priority for health economic analysis because of the relative low cost impact and the lack of available data. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.8.5 Evidence to recommendations

The aim of this topic was to determine the most effective management strategy for patients experiencing constipation as a result of strong opioid treatment.

The GDG considered the management of common opioid side effects, and the impact that management of these has on treatment adherence and pain control, to

be the most important outcomes. The GDG wanted to investigate the management of constipation by comparing the use of laxatives with switching opioid. However, no randomised trials were identified that looked at the interventions of interest.

The GDG noted that, despite the lack of evidence, recommendations were required on managing these common side effects in order to improve patient care. The group therefore agreed to make recommendations based on its clinical experience.

The GDG considered constipation to be a side effect that will affect nearly all patients taking strong opioid treatment and that this side effect will persist unless treated. The GDG therefore agreed that the best treatment would be to start laxatives when starting opioid treatment, and that laxative treatment should be optimised before switching opioids. However, given the lack of evidence, the GDG did not feel able to recommend a specific laxative or class of laxatives. The GDG was also aware that patients often do not understand that laxatives need to be taken regularly at the required dose to help with constipation or that laxatives take time to have an effect on constipation. It therefore recommended that patients be informed about these issues.

3.8.6 Recommendations on managing constipation

Recommendation 1.1.17

Inform patients that constipation affects nearly all patients receiving strong opioid treatment.

Recommendation 1.1.18

Prescribe laxative treatment (to be taken regularly at an effective dose) for all patients initiating strong opioids.

Recommendation 1.1.19

Inform patients that treatment for constipation takes time to work and adherence is important.

Recommendation 1.1.20

Optimise laxative treatment for the management of constipation before considering switching strong opioids.

3.9 Management of nausea

Nausea is defined as the unpleasant feeling of the need to vomit, often accompanied by autonomic symptoms. Opioids commonly cause nausea by several mechanisms: gastroparesis, constipation or through central effects on the brain. Prevalence rates of nausea in cancer patients taking opioids can be up to 40%.

For patients nearing the end of life, nausea causes significant psychological distress and can lead to reduced quality of life. Hospital and hospice admissions may be necessary to control symptoms, and parenteral rather than oral treatment regimens may have to be started.

For patients who need opioids, nausea and vomiting are dose-limiting adverse effects, and therefore their management can be seen as a prerequisite for effective pain management. Strategies to avoid nausea and vomiting when opioid treatment begins include prescribing a regular anti-emetic agent alongside the opioid. Strategies to address established nausea and vomiting in patients already taking opioids include anti-emetic medication, stopping or reducing opioids (including using non-opioid co-analgesics for 'opioid-sparing'), switching the opioid and changing the route of administration of the opioid.

The GDG rated the importance of this adverse effect as high, and felt that management of this common problem was inconsistent in both primary and secondary care settings. Potential sequelae of this common problem were felt to have a large effect on patients' quality of life and the involvement of healthcare providers.

3.9.1 Review question

Is anti-emetic treatment more effective with or without opioid switching in reducing nausea in patients with advanced and progressive disease who are taking strong opioids and experience nausea as a side effect?

3.9.2 Evidence review

This review question focused on the effectiveness of anti-emetics for the treatment of nausea resulting from strong opioids taken for pain by patients with advanced and progressive disease. Papers were included if they compared anti-emetic treatment with or without an associated switch in opioid in patients experiencing nausea from strong opioid treatment, in RCTs, or if they were systematic reviews of such trials:

However, the search identified no such papers.

3.9.3 Evidence statements

3.9.3.1 *No evidence was identified on the effectiveness of anti-emetic treatment with or without opioid switching in patients experiencing nausea as a side effect of strong opioid treatment.*

3.9.4 Health economic modelling

This topic was not considered a priority for health economic analysis because of the relative low cost impact and the lack of available data. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.9.5 Evidence to recommendations

The aim of this topic was to determine the most effective management strategy for patients experiencing nausea as a result of strong opioid treatment.

The GDG considered the management of common opioid side effects, and the impact that management of these has on treatment adherence and pain control, to be the most important outcomes. The GDG wanted to investigate the management of nausea by comparing the use of anti-emetics with switching opioid. However, no randomised trials were identified that looked at the interventions of interest.

The GDG noted that despite the lack of evidence, recommendations were required on managing these common side effects in order to improve patient care. The group therefore agreed to make recommendations based on its clinical experience.

The GDG noted that nausea tends to occur when starting strong opioid treatment or when increasing the dose of an opioid. In such cases, the nausea is normally transient and resolves without the need for medical intervention. However, many patients are not aware of this and may stop taking the opioid if they experience nausea. The GDG therefore agreed to make a recommendation that would raise patients' awareness about this.

The GDG was also aware that opinion is divided about prescription of routine anti-emetic treatment when starting or titrating opioids. Given the lack of evidence in this area, the GDG did not feel it was possible to make a definitive recommendation on this issue and so decided to recommend further research. The GDG agreed that if nausea is persistent and does not respond to anti-emetic treatment, switching opioids should be considered.

3.9.6 Recommendations and research recommendations on managing nausea

Recommendation 1.1.21

Advise patients that nausea may occur when starting strong opioid treatment or at dose increase, but that it is likely to be transient.

Recommendation 1.1.22

If nausea persists, prescribe and optimise anti-emetic treatment before considering switching strong opioids.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B2

Is prophylactic prescription of anti-emetic treatment or the availability of anti-emetic treatment at the patient's home more effective in reducing nausea than the availability of prescription on request for patients starting strong opioids for the treatment of pain in advanced or progressive disease? The outcomes of interest are nausea, time to control of nausea, patient acceptability of treatment, concordance and use of healthcare resources.

3.10 Management of drowsiness

Drowsiness is a common and sometimes serious adverse effect of opioid treatment in patients with advanced and progressive disease. The GDG defined drowsiness as a decreased level of consciousness characterised by sleepiness and difficulty in remaining alert but with easy arousal by stimuli. The degree of sedation in patients taking opioids can vary from mild sleepiness and fatigue to severe drowsiness or coma, and may be accompanied by other central nervous system side effects, such as hallucinations, cognitive impairment, agitation, myoclonus, respiratory depression and delirium.

The GDG felt that one of the most common problems encountered in the initial prescribing of opioids was drowsiness, and that it needed to be addressed. The question the group decided to focus on was whether opioid dose reduction or switching opioids would be more effective in reducing drowsiness.

Equivalent opioid dosage is calculated using conversion charts, and practice can vary regionally. This is further complicated by the fact that opioid dosage-equivalence can vary among individuals.

3.10.1 Review question

Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease who are taking strong opioids and experience drowsiness as a side effect?

3.10.2 Evidence review

This review question focused on the effectiveness of opioid switching and opioid dose reductions for the treatment of drowsiness resulting from strong opioids taken for pain by patients with advanced and progressive disease. Papers were included if they compared opioid dose reductions with opioid switching in patients experiencing drowsiness from strong opioid treatment in RCTs, or if they were systematic reviews of such trials.

However, the search identified no such papers.

3.10.3 Evidence statements

3.10.3.1 *No evidence was identified on the effectiveness of dose reduction compared with opioid switching in patients experiencing drowsiness as a side effect of strong opioid treatment.*

3.10.4 Health economic modelling

This topic was not considered a priority for health economic analysis because of the relative low cost impact and the lack of available data. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.10.5 Evidence to recommendations

The aim of this topic was to determine the most effective management strategy for patients experiencing drowsiness as a result of strong opioid treatment.

The GDG considered the management of common opioid side effects, and the impact that management of these has on treatment adherence and pain control, to be the most important outcomes. The GDG wanted to compare dose reduction with switching opioid for managing drowsiness. However, no randomised trials were identified that looked at the interventions of interest.

The GDG noted that, despite the lack of evidence, recommendations were required on managing this common side effect in order to improve patient care. The group therefore agreed to make recommendations based on its clinical experience.

The GDG noted that a significant proportion of patients taking strong opioids experience central side effects, such as drowsiness. The GDG was aware that if these side effects are experienced when starting strong opioid treatment or when doses of opioids are increased, they may be transient and may not require medical intervention to resolve. Therefore, the GDG decided to recommend that patients are informed of this.

However, the GDG agreed, based on its clinical experience, that if central side effects persist or are more severe, treatment by either opioid switching (if pain is not controlled) or dose reduction (if pain is controlled) is needed. The GDG also agreed that further research was needed to investigate the impact of early switching compared with dose reduction in patients experiencing persistent or severe central side effects because this has not been formally evaluated.

The GDG also agreed that when starting opioid treatment or at dose increase, patients may have impaired concentration which could affect their ability to undertake manual tasks such as driving. Since current formal guidance on whether patients should drive while taking opioids is unclear, and this query is frequently raised by patients, the GDG decided to recommend that potential impairment in relation to driving should always be discussed with the patient.

3.10.6 Recommendations and research recommendations on managing drowsiness

Recommendation 1.1.23

Advise patients that mild drowsiness or impaired concentration may occur when starting strong opioid treatment or at dose increase, but that it is often transient. Warn patients that impaired concentration may affect their ability to drive⁴ and undertake other manual tasks.

Recommendation 1.1.24

In patients with either persistent or moderate-to-severe central nervous system side effects:

- consider dose reduction if pain is controlled or
- consider switching opioids if pain is not controlled.

Recommendation 1.1.25

If side effects remain uncontrolled despite optimising therapy, consider seeking specialist advice.

⁴ <http://www.dft.gov.uk/dvla/medical/ata glance.aspx>

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B3

Is early switching of opioid, on development of side effects, more effective at reducing central side effects than persisting with current opioid and dose reduction in patients starting strong opioids? The outcomes of interest are time to clinically effective pain control with acceptable side effects.

4 Notes on the scope of the guideline

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is given in appendix C.

5 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG140).

6 Other versions of this guideline

6.1 *NICE pathway*

The recommendations from this guideline have been incorporated into a NICE pathway, which is available from <http://pathways.nice.org.uk/pathways/opioids-in-palliative-care>

6.2 *‘Understanding NICE guidance’*

A summary for patients and carers (‘Understanding NICE guidance’) is available from www.nice.org.uk/guidance/CG140/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2737).

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about strong opioids in advanced and progressive disease.

7 Related NICE guidance

Published

- Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guideline 96 (2010). Available from www.nice.org.uk/guidance/CG96
- Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE clinical guideline 95 (2010). Available from www.nice.org.uk/guidance/CG95
- Low back pain: early management of persistent non-specific low back pain. NICE clinical guideline 88 (2009). Available from www.nice.org.uk/guidance/CG88
- Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE clinical guideline 79 (2009). Available from www.nice.org.uk/guidance/CG79
- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008). Available from www.nice.org.uk/guidance/TA159
- Metastatic spinal cord compression: diagnosis and management of adults at risk of and with metastatic spinal cord compression. NICE clinical guideline 75 (2008). Available from www.nice.org.uk/guidance/CG75
- Osteoarthritis: the care and management of osteoarthritis in adults. NICE clinical guideline 59 (2008). Available from www.nice.org.uk/guidance/CG59
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGSP

8 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

9 References

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10 Glossary and abbreviations

10.1 Glossary

Adverse effects

Harmful or undesirable effects of an intervention.

Anti-emetic

A drug taken to prevent or treat nausea or vomiting.

Bioavailability

The amount of or rate at which a substance or drug is pharmaceutically available to, or active in, the body.

Background pain

Chronic persistent pain.

Breakthrough pain

A transient increase in pain intensity over background pain, typically of rapid onset and intensity, and generally self-limiting with an average duration of 30 minutes.

Concomitant medicine

Drugs that are given either at the same time or almost at the same time

Formulation

The process in which different chemical substances, including the active drug, are combined to produce a final medicinal product.

Health economic model

Mathematical and statistical techniques are used to synthesise the relevant costs and outcomes for part of a clinical pathway or a whole clinical pathway. Like most models, they typically represent a simplified view of reality. They are useful tools for decision makers who need to consider the costs and benefits associated with alternative courses of action. In particular, they are useful when decisions about the cost effectiveness of care depend on the effectiveness of multiple combinations of healthcare options (tests, treatment, long-term follow-up).

Immediate-release

A dosage form that is intended to release all the active ingredient on administration with no enhanced, delayed or extended release effect.

Imprecision

The results of quantitative studies with small samples and few events (and therefore wide confidence intervals) are imprecise.

Incremental cost-effectiveness ratio

The difference in the mean costs in the population of interest divided by the difference in the mean outcomes in the population of interest when comparing two interventions.

Indirectness

A type of comparison that may be carried out when a comparison of intervention A versus B is not available, but A was compared with C and B was compared with C. Such studies allow indirect comparisons of the magnitude of effect of A versus B.

Life year

A measure of health outcome that shows the number of years of remaining life expectancy.

Maintenance treatment

The various kinds of treatment (usually medical) given to patients to enable them to maintain their health in a disease-free, or limited-disease, state.

Network meta-analysis

A type of meta-analysis that takes into account both direct and indirect comparisons between interventions of interest (see also **Indirectness**).

Open-label

A term used to describe the situation when both the researcher and the participant in a research study know the treatment the participant is receiving. Open-label is the opposite of double-blind when neither the researcher nor the participant knows what treatment the participant is receiving.

Opioid

A chemical substance that has a morphine-like action in the body. The main purpose of use is for pain relief.

Palliative care

The active holistic care of patients with advanced, progressive illness; that is, the management of pain and other symptoms, and the provision of psychological, social and spiritual support. The goal of palliative care is achievement of the best quality of life for patients and families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments.

Pharmacokinetics

The process by which a drug is absorbed, distributed, metabolised and eliminated by the body.

Preparation

A final pharmaceutical product which contains an active drug plus the added ingredients such as stabilisers, flavourings or coatings to enable the drug and dose to be delivered in an accurate and replicable way as stated in the Summary of Product Characteristics.

Rescue dose

The dose of an analgesic required for the relief of **breakthrough pain**.

Sensitivity analyses

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. The different types of sensitivity analysis are:

- One-way sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequence of each parameter on the results of the study.
- Multi-way sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.

- Threshold sensitivity analysis: the critical values of parameters above or below which the conclusions of the study will change are identified.
- Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques.

Stable pain

Pain that is predictable in its pattern and intensity, and which requires regular analgesia that can be planned in a non-urgent context.

Strong opioid

Morphine-like drugs (eg diamorphine, fentanyl, oxycodone, buprenorphine). Codeine and dihydrocodeine are weak opioids.

Subcutaneous injections

A subcutaneous injection is given in the fatty layer of tissue just under the skin.

Sublingual

Underneath the tongue.

Sustained-release

Designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimal side effects.

Transdermal patch

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

Transient

For a short time only; of short duration; temporary or transitory.

Titration

Incremental increase in drug dosage to a level that provides the optimal therapeutic effect.

Toxicity

The degree to which a substance can harm humans or animals.

Unstable pain

Pain that is unpredictable in its pattern and intensity, and which requires irregular analgesia in an urgent context.

Please see the NICE glossary (www.nice.org.uk/website/glossary/glossary.jsp) for an explanation of terms not described above.

10.2 Abbreviations

Abbreviation	Term
BNF	British National Formulary
CI	Confidence interval
EAPC	European Association for Palliative Care
FBT	Fentanyl buccal tablet
FPNS	Fentanyl pectin nasal spray
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HE	Health economics
ICER	Incremental cost-effectiveness ratio
INFS	Intranasal fentanyl spray
IR	Immediate release
OTFC	Oral transmucosal fentanyl citrate
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
RCT	Randomised control trial
QALD	Quality-adjusted life days
QALY	Quality-adjusted life years
QoL	Quality of life
SR	Sustained release
SIGN	Scottish Intercollegiate Guideline Network

Appendix A Contributors and declarations of interests

The Guideline Development Group

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The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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Declarations of interests

Dr Damien Longson (Chair): No interests declared.

Dr Catherine Stannard: No interests declared.

Professor Mike Bennett: Received fee for masterclass on neuropathic pain assessment. Funded by Pfizer. Classified as personal pecuniary non-specific.

Mrs Catherine Piggin: No interests declared.

Dr Lindsay Smith: No interests declared.

Dr Joy Ross: No interests declared.

Dr Mark Taubert: No interests declared.

Mrs Margaret Gibbs: No interests declared.

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Mrs Natalie Laine: No interests declared.

Ms Vivien Pipe: No interests declared.

Appendix B List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

B1 Communication

What are the most clinically effective and cost-effective methods of addressing patient and carer concerns about strong opioids, including anticipating and managing adverse effects, and engaging patients in prescribing decisions?

Why this is important

We know from qualitative work that patients do not always understand how to take strong opioids or the difference between sustained-release and rescue medication. Patients, their carers and some clinicians fear the adverse effects of these drugs and believe that strong opioids, especially morphine, can be negatively associated with adverse effects and death. To improve adherence and to enable patients and carers to benefit from the proven analgesic effects of strong opioids, research should be undertaken to determine how to address the main concerns of patients, the level of information they require and the best time and methods to deliver this. The benefits of greater involvement in this process by specialist nurses or pharmacists should also be examined in research.

B2 Side effects

Is prophylactic prescription of anti-emetic treatment or availability of anti-emetic treatment at the patient's home more effective in reducing nausea than the availability of prescription on request for patients starting strong opioids for the treatment of pain in advanced or progressive disease? The outcomes of interest are nausea, time to control of nausea, patient acceptability of treatment, concordance and use of healthcare resources.

Why this is important

Patients may experience transient nausea when starting opioid treatment and opioid-induced nausea often responds to anti-emetic treatment. When nausea occurs, timely review by a healthcare professional to start anti-emetic treatment can be difficult to achieve in the community setting. Prescription of routine anti-emetic treatment when starting opioids is controversial. It is important to evaluate the positive and negative impact of this strategy; while it may reduce opioid-induced nausea, improve adherence with opioid treatment, and reduce use of healthcare resources, the added burden to the patient and overall cost effectiveness are currently unclear.

B3 Side effects

Is early switching of opioid, on development of side effects, more effective at reducing central side effects than persisting with current opioid and dose reduction in patients starting strong opioids? The outcomes of interest are time to clinically effective pain control with acceptable side effects.

Why this is important

The common gastrointestinal opioid-induced side effects such as constipation or nausea can often be managed with concomitant medications. A significant proportion of patients starting strong opioids experience central side effects that patients report as distressing and often limit daily activities. Although central side effects may be transient, persistent symptoms can be difficult to treat and cause significant morbidity. The clinical strategy of opioid switching has been shown to reduce central side effects. The impact of early switching, rather than dose reduction or a 'watch and wait' strategy has not been formally evaluated but may improve both time to opioid response and health-related quality of life.

Appendix C Guideline scope

Guideline title

Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults

Short title

Opioids for pain in palliative care

The remit

The Department of Health has asked NICE to produce a short clinical guideline on: 'safe and effective prescribing of strong opioids in palliative care of adults'.

Clinical need for the guideline

Current practice

- a) Each year more than 155,000 people in the UK die of cancer, and to this figure can be added deaths from heart failure, kidney, liver and respiratory disease, and from neurodegenerative conditions. Many people with these conditions will develop pain for which a strong opioid is needed.
- b) The recently updated World Cancer Declaration includes a target to make effective pain control more accessible. Several key documents recognise the importance of effective pain control, including 'Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance 2004), 'Control of pain in adults with cancer' (Scottish Intercollegiate Guidelines Network guideline 106), and 'A strategic direction for palliative care services in Wales' (Welsh Assembly Government 2005).
- c) Pain is common in advanced and progressive disease. Up to two-thirds of people with cancer experience pain that needs a strong opioid. This proportion is similar or higher in many other advanced and progressive conditions.
- d) Strong opioids, especially morphine, are the principal treatments for pain related to advanced and progressive disease, and their use has increased significantly in the primary care setting. However, the pharmacokinetics of the various opioids are very different and there are marked differences in bioavailability, metabolism and response between patients. A suitable opioid must be selected for each patient and, because drug doses cannot be estimated or calculated in advance, the dose must be individually titrated. Ensuring that this selection and titration is done effectively and safely has a major impact on patient comfort. The World Health Organization has produced a pain ladder for the relief of cancer pain and strong opioids are represented on the third level of the three-step ladder.
- e) Misinterpretations and misunderstanding have surrounded strong opioids for decades, and these are only slowly being resolved. Until recently, many sources for prescribing advice have given varying and sometimes conflicting advice. These factors, along with the wide range of formulations and preparations, have resulted in errors causing underdosing and avoidable pain, or overdosing and distressing adverse effects. Despite repeated warnings, these problems have led on occasion to patient deaths, and resulted in doctors facing the General Medical Council or court proceedings.
- f) This guideline will clarify the clinical pathway, and help to improve pain management and patient safety. The target audience will be non-specialist

healthcare professionals initiating strong opioids for pain in adults with advanced and progressive disease. However, the guideline is likely to be of relevance to palliative care specialists as well.

The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

- a) Adults (18 years and older) with advanced and progressive disease⁵, who require strong opioids for pain control.
- b) No patient subgroups have been identified as needing specific consideration.

Groups that will not be covered

- a) Children (younger than 18 years).
- b) Adults without advanced and progressive disease.
- c) Adults who have not yet had a pain assessment to check whether strong opioids are required.

Healthcare setting

- a) All settings in which care commissioned by the NHS is provided, including hospices, care homes and the community.

Clinical management

Key clinical issues that will be covered

- a) First-line treatment with strong opioids considering:
 - titration schedule
 - formulation
 - routes of administration
 - breakthrough pain.
- b) Management strategies for side effects (including switching opioid).
- c) Information for patients and carers about consenting to treatment and monitoring effectiveness.

Clinical issues that will not be covered

- a) Pain assessment before starting strong opioid therapy.
- b) Non-opioid pain control.
- c) Care during the last days of life (for example, while on the Liverpool Care Pathway).

⁵ Such as cancer, heart disease, liver disease, lung disease, kidney disease, HIV and terminal neurodegenerative or neuromuscular conditions.

Main outcomes

- a) Pain.
- b) Opioid side effects.
- c) Adverse events.
- d) Health-related quality of life.

Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

Status

Scope

This is the final scope.

Timing

The development of the guideline recommendations will begin in July 2011.

Related NICE guidance

- Neuropathic pain. NICE clinical guideline 96 (2010). Available from www.nice.org.uk/guidance/CG96
- Chest pain of recent onset. NICE clinical guideline 95 (2010). Available from www.nice.org.uk/guidance/CG95
- Low back pain. NICE clinical guideline 88 (2009). Available from www.nice.org.uk/guidance/CG88
- Rheumatoid arthritis. NICE clinical guideline 79 (2009). Available from www.nice.org.uk/guidance/CG79
- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008). Available from www.nice.org.uk/guidance/TA159
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- Osteoarthritis. NICE clinical guideline 59 (2008). Available from www.nice.org.uk/guidance/CG59
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGSP

Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix D How this guideline was developed

See separate file.

Appendix E Evidence tables

See separate file.

Appendix F Full health economic report

See separate file.

Opioids in palliative care:
safe and effective prescribing of strong
opioids for pain in palliative care of
adults

Appendix D – How this guideline was developed
May 2012

Developed for NICE by the National Collaborating Centre for Cancer
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How this guideline was developed

This guideline was developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

The majority of the clinical questions posed in this guideline are interventional questions. For these questions the eligible studies were restricted to randomised controlled trials or systematic reviews thereof. Such studies were included whether they were published in full or as abstracts only. This decision was made in order to include all high level evidence. However, when such evidence was published in abstract form only, full appraisal and reporting of these studies was hampered by a lack of information and this was always highlighted to the GDG. Moreover, due to a lack of evidence, studies that were not on first-line treatment were also included, and when this was the case, it was also highlighted to the GDG.

Search strategies

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in 'The guidelines manual' (2009). The aim of the systematic searches was to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group and Short Clinical Guidelines Technical Team.

The search strategies for the review questions were developed by the Information Services Team with advice from the Clinical Guidelines Technical Team. Structured questions were developed using the PICO (population, intervention, comparison, outcome) model and translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches.

The NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched for economic evaluations. Search filters for economic evaluations and quality of life studies were used on bibliographic databases. There were no date restrictions imposed on the searches.

Guideline Development Group members were also asked to alert the Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between May 2011 and August 2011.

Guidance/guidelines	Systematic reviews/economic evaluations
British Pain Society	Cochrane Database of Systematic Reviews
Cochrane Library	Embase
Embase	Health Economic Evaluations Database
Guidelines and Audit Implementation	Medline

Network	
Health Technology Assessments	NHS Economic Evaluations Database
Medline	NHS Evidence
National Comprehensive Cancer Network	
National Guideline Clearinghouse (US)	
National Institute for Health and Clinical Excellence (NICE)	
National Institute of Health Research (NIHR)	
NHS Evidence	
Scottish Intercollegiate Guidelines Network	
World Health Organization	

Main searches

The following sources were searched for the topics presented in the sections below.

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (CRD)
- Health Technology Assessment Database – HTA (CRD)
- CINAHL (EBSCO)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PsycInfo
- Web of Science (Science Citation Index, Social Science Citation Index, ISI Conference Proceedings)

Systematic reviews and mapping searches

The first search was conducted in June 2011 and looked for systematic reviews and primary studies (the ‘mapping search’ with no methodological filter applied) to answer questions about first line treatment with strong opioids.

The MEDLINE search strategies are presented below. They were translated for use in each of the other databases.

Ovid MEDLINE <1950 to2011>

The patient information search was conducted in May 2011

Information for patients and carers about consenting to treatment and monitoring effectiveness.

Ovid MEDLINE <1950 to 2011>

1. exp Analgesics, Opioid/
2. Alfentanil/ or (alfentanil or alfentanyl or alphentanil or alphentanil or rapifen).tw.
3. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
4. (Dipipanone or Pipadone).tw.
5. Exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
6. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
7. Hydromorphone/ or (hydromorphon\$ or palladone or dilaudid or dihydromorphinone).tw.
8. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
9. Methadone/ or (methadone or dolophine).tw.
10. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
11. Oxycodone/ or (oxycodone or oxycontin).tw.
12. Oxymorphone/ or (oxymorphone or numorphan).tw.
13. Pentazocine/ or pentazocine.tw.
14. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
15. opioid\$.tw.
16. or/1-15
17. choice behavior/
18. decision making/
19. exp decision support techniques/
20. ((patient\$ or consumer\$) adj3 (decision\$ or choice or preference or participation)).tw.
21. ((personal or interpersonal or individual) adj3 (decision\$ or choice or preference\$ or participat\$)).tw.
22. (decision\$ adj3 (aid\$ or support\$)).tw.
23. or/17-22
24. exp Patient Participation/
25. Pamphlets/
26. exp Audiovisual Aids/
27. (video\$1 or dvd\$).tw.
28. exp Internet/
29. exp Self-Help Groups/
30. (support\$ adj2 (group\$ or meet\$)).tw.
31. exp Patient Education/mt
32. ((inform\$ or support\$) adj2 (tool\$ or method\$ or group\$)).tw.
33. or/24-32
34. (information adj2 (need\$ or support\$)).tw.
35. (information adj2 (leaflet\$ or booklet\$ or pack\$ or material\$)).tw.
36. 34 or 35
37. 23 or 33 or 36
38. 16 and 37

First-line treatment with strong opioids considering:

- titration schedule
- formulation
- routes of administration
- breakthrough pain.

1. exp Analgesics, Opioid/

2. Alfentanil/ or (alfentanil or alfentanyl or alphentanyl or alphentanil or rapifen).tw.
 3. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
 4. (Dipipanone or Pipadone).tw.
 5. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
 6. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
 7. Hydromorphone/ or (hydromorphon\$ or palladone or dilaudid or dihydromorphinone).tw.
 8. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
 9. Methadone/ or (methadone or dolophine).tw.
 10. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
 11. Oxycodone/ or (oxycodone or oxycontin).tw.
 12. Oxymorphone/ or (oxymorphone or numorphan).tw.
 13. Pentazocine/ or pentazocine.tw.
 14. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
 15. (opioid\$ or opiate\$).tw.
 16. or/1-15
 17. breakthrough pain.tw.
 18. spontaneous pain.tw.
 19. incident\$ pain.tw.
 20. ((transitory or transient) adj pain).tw.
 21. episodic pain.tw.
 22. or/17-21
 23. 16 and 22
-
1. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
 2. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
 3. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
 4. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
 5. Oxycodone/ or (oxycodone or oxycontin).tw.
 6. (opioid\$ or opiate\$).tw.
 7. or/1-6
 8. exp Chemistry, Pharmaceutical/
 9. formulat\$.tw.
 10. ((immediate or non-sustained) adj2 release).tw.
 11. Delayed-Action Preparations/
 12. ((sustained or modified or slow or controlled or continuous or prolonged or extended) adj release).tw.
 13. or/8-12
 14. 7 and 13
-
1. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
 2. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
 3. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
 4. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
 5. Oxycodone/ or (oxycodone or oxycontin).tw.
 6. (opioid\$ or opiate\$).tw.
 7. or/1-6
 8. exp Administration, Oral/

9. exp Administration, Cutaneous/
 10. exp Infusions, Subcutaneous/
 11. (transdermal or trans-dermal or patch\$ or cream\$ or ointment\$ or unguent\$).tw.
 12. ((percutaneous or dermal or cutaneous or skin or topical\$ or transcutaneous or trans-cutaneous) adj2 (administ\$ or deliver\$ or route\$ or method\$)).tw.
 13. ((oral\$ or mouth) adj2 (administ\$ or deliver\$ or route\$ or method\$)).tw.
 14. ((subcutaneous\$ or infusion\$ or implant\$ or hypoderm\$ or parenteral\$) adj2 (administ\$ or deliver\$ or route\$ or method\$)).tw.
 15. or/8-14
 16. 7 and 15
-
1. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
 2. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
 3. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
 4. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
 5. Oxycodone/ or (oxycodone or oxycontin).tw.
 6. (opioid\$ or opiate\$).tw.
 7. or/1-6
 8. exp Administration, Oral/
 9. exp Administration, Cutaneous/
 10. exp Infusions, Subcutaneous/
 11. (transdermal or trans-dermal or patch\$ or cream\$ or ointment\$ or unguent\$).tw.
 12. ((percutaneous or dermal or cutaneous or skin or topical\$ or transcutaneous or trans-cutaneous) adj2 (administ\$ or deliver\$ or route\$ or method\$)).tw.
 13. ((oral\$ or mouth) adj2 (administ\$ or deliver\$ or route\$ or method\$)).tw.
 14. ((subcutaneous\$ or infusion\$ or implant\$ or hypoderm\$ or parenteral\$) adj2 (administ\$ or deliver\$ or route\$ or method\$)).tw.
 15. or/8-14
 16. 7 and 15

Management strategies for side effects (including switching opioid).

nausea and vomiting:

1. Alfentanil/ or (alfentanil or alfentanyl or alphentanyl or alphentanil or rapifen).tw.
2. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
3. (Dipipanone or Pipadone).tw.
4. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
5. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
6. Hydromorphone/ or (hydromorphon\$ or palladone or dilaudid or dihydromorphinone).tw.
7. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
8. Methadone/ or (methadone or dolophine).tw.
9. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
10. Oxycodone/ or (oxycodone or oxycontin).tw.
11. Oxymorphone/ or (oxymorphone or numorphan).tw.
12. Pentazocine/ or pentazocine.tw.
13. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
14. (opioid\$ or opiate\$).tw.

15. or/1-14
16. exp Antiemetics/
17. (antiemetic\$ or anti emetic\$ or anti-emetic\$ or anti-nause\$ or anti nause\$ or emetogen\$).tw.
18. 16 or 7
19. 15 and 18

drowsiness:

1. Alfentanil/ or (alfentanil or alfentanyl or alphentanil or alphentanil or rapifen).tw.
2. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
3. (Dipipanone or Pipadone).tw.
4. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
5. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
6. Hydromorphone/ or (hydromorphon\$ or palladone or dilaudid or dihydromorphinone).tw.
7. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
8. Methadone/ or (methadone or dolophine).tw.
9. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
10. Oxycodone/ or (oxycodone or oxycontin).tw.
11. Oxymorphone/ or (oxymorphone or numorphan).tw.
12. Pentazocine/ or pentazocine.tw.
13. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
14. (opioid\$ or opiate\$).tw.
15. or/1-14
16. Lethargy/
17. (drows\$ or sleepiness or sleepy or letharg\$ or somnolen\$ or sluggish or indolen\$).tw.
18. 16 or 17
19. 15 and 18

constipation:

1. exp Analgesics, Opioid/
2. Alfentanil/ or (alfentanil or alfentanyl or alphentanil or alphentanil or rapifen).tw.
3. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
4. (Dipipanone or Pipadone).tw.
5. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
6. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
7. Hydromorphone/ or (hydromorphon\$ or palladone or dilaudid or dihydromorphinone).tw.
8. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
9. Methadone/ or (methadone or dolophine).tw.
10. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
11. Oxycodone/ or (oxycodone or oxycontin).tw.
12. Oxymorphone/ or (oxymorphone or numorphan).tw.
13. Pentazocine/ or pentazocine.tw.
14. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
15. (opioid\$ or opiate\$).tw.
16. or/1-15
17. exp Laxatives/

18. (laxative\$ or laxation).tw.
19. purgative\$.tw.
20. aperient\$.tw.
21. cathartic\$.tw.
22. (evacuative\$ or evacuant\$).tw.
23. costive\$.tw.
24. (bulking agent\$ or osmotic agent\$ or enterokinetic agent\$).tw.
25. ((stool\$ or faecal or fecal) adj soften\$).tw.
26. or/17-25
27. 16 and 26

Economic search

The following sources were searched to identify economic evaluations and quality of life data featuring the patient population of Topic 1.

- Medline
- Embase
- NHSEED
- HTA
- HEED

Search of economic-sepcific database:

The first search was conducted in June 2011 and looked for economic studies to answer questions about first line treatment with strong opioids (Topic 1).

The NHS-EED and HTA search strategies are presented below. They were translated for use in HEED.

Not date restriction have been applied to NHS-EED, HTA and HEED.

1. Analgesics, Opioid
or Opioid Analgesics
or Opioids
2. Alfentanil
or Alfentanil Hydrochloride
or Esteve Brand of Alfentanil Hydrochloride
or ICI Brand of Alfentanil Hydrochloride
or Janssen Brand of Alfentanil Hydrochloride
3. Buprenorphine
or Buprenorphine Hydrochloride
or Essex Brand of Buprenorphine Hydrochloride
or Grünenthal Brand of Buprenorphine
or Grünenthal Brand of Buprenorphine Hydrochloride
or Key Brand of Buprenorphine Hydrochloride
or Reckitt & Colman Brand 1 of Buprenorphine Hydrochloride
or Reckitt & Colman Brand 2 of Buprenorphine Hydrochloride
or Reckitt Benckiser Brand of Buprenorphine Hydrochloride
or Reckitt Brand of Buprenorphine Hydrochloride
or Schering-Plough Brand of Buprenorphine Hydrochloride
4. Heroin
or APS Brand of Heroin Hydrochloride
or Evans Vaccines Brand of Heroin Hydrochloride

- or Heroin Hydrochloride
- 5. Fentanyl
 - or Cephalon Brand of Fentanyl Buccal OraVescent
 - or Fentanyl Citrate
 - or Janssen Pharmaceutica Brand of Fentanyl
- 6. Hydromorphone
 - or Hydromorphone Hydrochloride
- 7. Meperidine
 - or Meperidine Hydrochloride
- 8. Methadone
 - or addiCare Brand of Methadone Hydrochloride
 - or Biomet Brand of Methadone Hydrochloride
 - or Esteve Brand of Methadone Hydrochloride
 - or Generics Brand of Methadone Hydrochloride
 - or GlaxoSmithKline Brand of Methadone Hydrochloride
 - or Mallinckrodt Brand of Methadone Hydrochloride
 - or Martindale Brand of Methadone Hydrochloride
 - or Methadone Hydrochloride
 - or Pharmascience Brand of Methadone Hydrochloride
 - or Pinewood Brand of Methadone Hydrochloride
 - or Rosemont Brand of Methadone Hydrochloride
 - or Roxane Brand of Methadone Hydrochloride
 - or Yamanouchi Brand of Methadone Hydrochloride
- 9. Morphine
 - or Morphine Chloride
 - or Morphine Sulfate
 - or Morphine Sulfate (2:1), Anhydrous
 - or Morphine Sulfate (2:1), Pentahydrate
- 10. Oxycodone
 - or Oxycodone Hydrochloride
- 11. Oxymorphone
 - or Bristol-Myers Squibb Brand of Oxymorphone Hydrochloride
 - or Endo Brand of Oxymorphone Hydrochloride
 - or Oxymorphone Hydrochloride
- 12. Pentazocine
 - or Pentazocine Hydrochloride
 - or Pentazocine Lactate
- 13. Remifentanil
 - or remifentanyl
 - or remiphentanyl
 - or remiphentanil

Review questions and review protocols

Review questions

- **What information do patients with advanced and progressive disease who require strong opioids, or their carers need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid.**
- **What is the most effective first-line opioid treatment in patients with advanced and progressive disease who require strong opioids?**
- Is immediate-release opioids (morphine/oxycodone) more effective than sustained-release opioids (morphine/oxycodone) or transdermal patches (fentanyl/buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?
- Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl/buprenorphine) as first-line maintenance therapy for pain in patients with advanced and progressive disease who require strong opioids?
- Is transdermal fentanyl patches more effective than transdermal buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
- Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
- Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
- What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)?
- **What is the most effective management of side effects of strong opioids?**
- Is laxative treatment more effective with or without opioid switching in reducing constipation in patients with advanced and progressive disease who are taking strong opioids and experience constipation as a side effect?
- Is anti-emetic treatment more effective with or without opioid switching in reducing nausea in patients with advanced and progressive disease who are taking strong opioids and experience nausea as a side effect?
- Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect?

Review protocols

Review question 1	What information do patients with advanced and progressive disease who require strong opioids, or their carers need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid.
Objectives	To ascertain what information patients and carers have found to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.
Inclusion/Exclusion criteria	This question is a qualitative question and the evidence was therefore focused on qualitative studies reporting information that patients and/or carers have found to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. Additional databases will include: CINAHL and PsycInfo. An animals studies filter will be applied.
The review strategy	The best evidence will come from qualitative studies reporting information that patients have found to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.
POPULATION	Adult patients with advanced and progressive disease who need strong opioids or their carers
SITUATION	Information needs associated with consenting to opioid treatment and monitoring the effectiveness and side effects of the opioid.
TIMING	At the time of considering consenting to opioid treatment and during strong opioid therapy.
OUTCOMES	Information reported by patients/carers to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.

Review question 2a	Is immediate-release opioids (morphine/oxycodone) more effective than sustained-release opioids (morphine/oxycodone) or transdermal patches (fentanyl/buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?
Objectives	To estimate the effectiveness of immediate-release morphine/oxycodone versus sustained-release morphine/oxycodone or versus fentanyl/buprenorphine patches .

Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing immediate-release morphine/oxycodone either to sustained-release morphine/oxycodone or to fentanyl/buprenorphine patches in patients with advanced and progressive disease who require strong opioids for pain.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line immediate-release morphine/oxycodone to first-line sustained-release morphine/oxycodone, and fentanyl/buprenorphine patch, respectively, for pain in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to IR and SR drug (morphine, oxycodone), patch (fentanyl, buprenorphine) and population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids for pain and who are suitable for oral opioid treatment.
INTERVENTION	Immediate release opioid (morphine/oxycodone)
COMPARATORS	Sustained release opioid (morphine or oxycodone) Patch formulation (Fentanyl/Buprenorphine)
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2b	Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl/buprenorphine) as first-line maintenance therapy for pain in patients with advanced and progressive disease who require strong opioids?
Objectives	To estimate the effectiveness of sustained-release morphine versus sustained-release oxycodone or versus fentanyl/buprenorphine patches .
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing sustained-release morphine either

	to sustained-release oxycodone or to fentanyl/buprenorphine patches in patients with advanced and progressive disease who require strong opioids for pain.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line sustained-release morphine to first-line sustained-release oxycodone, fentanyl patch and buprenorphine patch, respectively, for pain in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids and who are suitable for oral opioid treatment.
INTERVENTION	Sustained release morphine
COMPARATORS	Sustained release oxycodone Fentanyl patch Buprenorphine patch
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life Percentage of people who achieve pain relief with no/minor side effects/adverse events, -Percentage of people who achieve pain relief with moderate side effects/adverse events, -Percentage of people who do not achieve pain relief with no/minor side effects/adverse events, - Percentage of people who do not achieve pain relief with severe side effects/adverse events.

Review question 2c	Is transdermal fentanyl patches more effective than transdermal buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
Objectives	To estimate the effectiveness of fentanyl patches versus buprenorphine patches.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing fentanyl patches to buprenorphine patches in patients with advanced and progressive disease who require strong

	opioids for pain and who are not suitable for oral treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line fentanyl patches to buprenorphine patches for pain in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.
INTERVENTION	Fentanyl patch
COMPARATORS	Buprenorphine patch
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2d	Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
Objectives	To estimate the effectiveness of subcutaneous morphine versus subcutaneous diamorphine and/or subcutaneous oxycodone.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing subcutaneous morphine to subcutaneous diamorphine or to subcutaneous oxycodone in patients with advanced and progressive disease who require strong opioids for pain and who are not suitable for oral treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line subcutaneous morphine to first-line subcutaneous diamorphine and/or subcutaneous oxycodone, for pain in a randomised population of patients with

	advanced and progressive disease who require strong opioids but are not suitable for oral opioid treatment. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.
INTERVENTION	Subcutaneous morphine
COMPARATORS	Subcutaneous diamorphine Subcutaneous oxycodone
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2e	Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
Objectives	To estimate the effectiveness of the best patch opioid (as established in question 1c) versus the best subcutaneous opioid (as established in question 1d).
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing the best patch opioid to the best subcutaneous opioid in patients with advanced and progressive disease who require strong opioids for pain and who are not suitable for oral treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing the best first-line patch (as shown in question 1c) to the best first-line subcutaneous opioid (as shown in question 1d) for pain in a randomised population of patients with advanced and progressive disease who require strong opioids but are not suitable for oral opioid treatment. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).

POPULATION	Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.
INTERVENTION	Best patch
COMPARATORS	Best Subcutaneous
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2f	What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)?
Objectives	To estimate the effectiveness of immediate-release morphine versus fast-acting fentanyl and immediate-release oxycodone.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing immediate-release morphine to fast-acting fentanyl or to immediate-release oxycodone in patients with advanced and progressive disease who experience breakthrough pain and who are currently treated with strong opioids for background pain
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing immediate-release morphine to fast-acting fentanyl or immediate-release oxycodone, respectively, for breakthrough pain in a randomised population of patients with advanced and progressive disease who experience breakthrough pain and who are currently treated with strong opioids for background pain. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the fentanyl preparation (buccal, sublingual, intranasal, transmucosal) and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who experience breakthrough pain and who are currently treated with first-line opioids for background pain
INTERVENTION	Immediate release morphine

COMPARATORS	Fast acting fentanyl (buccal, sublingual, intranasal, transmucosal) Immediate release (oral) oxycodone
OUTCOMES	Breakthrough pain Background pain? Opioid side effects Adverse events Health-related quality of life

Review question 3a	Is laxative treatment with or without opioid switching more effective in reducing constipation in patients with advanced and progressive disease on strong opioids who experience constipation as a side effect?
Objectives	To estimate the effectiveness of laxative treatment + opioid switch versus laxative treatment in patients with advanced and progressive disease who experience constipation from treatment with strong opioids.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing laxative treatment + opioid switch to laxative treatment in patients with advanced and progressive disease who experience constipation as a side effect of strong opioid treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials comparing laxatives with and without an associated switch in the strong opioid used for background pain relief in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the type of laxative used and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease on strong opioids who experience constipation.
INTERVENTION	Laxative + switching opioid
COMPARATORS	Laxative
OUTCOMES	Constipation Treatment compliance Pain

Review question 3b	Is anti-emetic treatment with or without opioid switching more effective in reducing nausea in patients with advanced and progressive disease on strong opioids who experience nausea as a side effect?
Objectives	To estimate the effectiveness of anti-emetic treatment + opioid switch versus anti-emetic treatment in patients with advanced and progressive disease who experience nausea from treatment with strong opioids.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing anti-emetic treatment + opioid switch to anti-emetic treatment in patients with advanced and progressive disease who experience nausea as a side effect of strong opioid treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials comparing anti-emetics with and without an associated switch in the strong opioid used for background pain relief in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the type of anti-emetic used and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease on strong opioids who experience nausea.
INTERVENTION	Anti-emetic + switching opioid
COMPARATORS	Anti-emetic
OUTCOMES	Nausea Vomiting Treatment compliance Pain

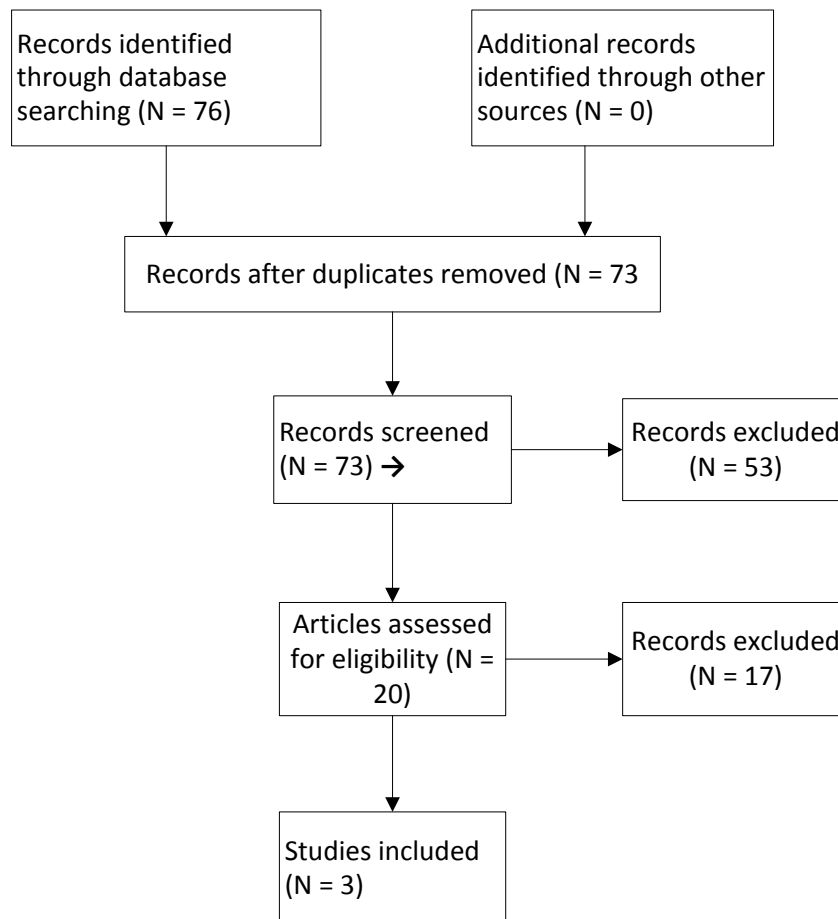
Review question 3c	Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect?
Objectives	To estimate the effectiveness of opioid dose reductions versus opioid switching in patients with advanced and progressive disease who experience drowsiness from treatment with strong opioids.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing opioid dose reductions to opioid

	switches in patients with advanced and progressive disease who experience drowsiness as a side effect of strong opioid treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials that compare opioid dose reductions with opioid switching in randomised populations. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the amount of dose reduction and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease on strong opioids who experience drowsiness.
INTERVENTION	Reduce dose of opioid
COMPARATORS	Switch opioid
OUTCOMES	Drowsiness Treatment compliance Pain

Excluded studies

Flow diagram of excluded studies for review Question 1

What information do patients with advanced and progressive disease who require strong opioids, or their carers need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid.



Excluded studies:

Questions and answers about pain control: a guide for people with cancer and their families. -76. 1995. Rockville, MD, United States Department of Health and Human Services Public Health Service.

Excl reason: Patient information material

Information from your family doctor. Chronic pain medicines. American Family Physician 69[5], 1197-1198. 1-3-2004.

Excl reason: Patient information on internet with no referenced evidence base.

Intervention reduces chronic pain visits. ED Management 22[12], 141-142. 2010.

Excl reason: Not in PICO

Alonso Herreros, J. M., Najera Perez, M. D., Vazquez, Polo A., Soler, Soler M., and Vila, Clerigues N. Dispensing medical drugs and official preparations to outpatients: Information to the patient. [Spanish]. Farmacia Hospitalaria 20[5], 308-313. 1996.

Excl reason: Not in PICO

Anderson, K. O., Richman, S. P., Hurley, J., Palos, G., Valero, V., Mendoza, T. R., Gning, I., and Cleeland, C. S. Cancer pain management among underserved minority outpatients: Perceived needs and barriers to optimal control. *Cancer* 94[8], 2295-2304. 2002.

Excl reason: Not in PICO

Anderson, K. O., Cohen, M. Z., Mendoza, T. R., Guo, H., Harle, M. T., and Cleeland, C. S. Brief cognitive-behavioral audiotape interventions for cancer-related pain: Immediate but not long-term effectiveness. *Cancer* 107[1], 207-214. 1-7-2006.

Excl reason: Not in PICO

Arnstein, P. Chronic neuropathic pain: issues in patient education. *Pain Management Nursing* 5[4], 34-41. 2-12-2004.

Excl reason: Not in PICO

Aubin, M., Vezina, L., Parent, R., Fillion, L., Allard, P., Bergeron, R., Dumont, S., and Giguere, A. Impact of an educational program on pain management in patients with cancer living at home. *Oncology Nursing Forum* 33[6], 1183-1188. 2006.

Excl reason: Not in PICO

Barlési, F., Duffaud, F., Doddoli, C., Gimenez, C., Auquier, P., Favre, R., and Kleisbauer, J. P. [Impact of a brochure on pain destined for thoracic oncology patients] [French]. *Presse Medicale* 33[19 pt 1], 1313-1318. 2004.

Excl reason: Not in PICO

Bingel, U., Wanigasekera, V., Wiech, K., Mhuirheartaigh, R. N., Lee, M. C., Ploner, M., and Tracey, I. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanyl. *Science Translational Medicine* 3[70], 70ra14. 2011.

Excl reason: Not in PICO

Binhas, M., Roudot-Thoraval, F., Thominet, D., Maison, P., and Marty, J. Impact of written information describing postoperative pain management on patient agreement with proposed treatment. *European Journal of Anaesthesiology* 25[11], 884-890. 2008.

Excl reason: Not in PICO

Borgsteede, Sander D., Karapinar-larkit, Fatma, Hoffmann, Emmy, Zoer, Jan, and van den Bemt, Patricia M. L. A. Information needs about medication according to patients discharged from a general hospital. *Patient Education and Counseling* 83[1], 22-28. 2011.

Excl reason: Not in PICO

Bozimowski, Greg. Patient Perceptions of Pain Management Therapy: A Comparison of Real-Time Assessment of Patient Education and Satisfaction and Registered Nurse Perceptions. *Pain Management Nursing* In Press. 2011.

Excl reason: Not in PICO

Buchanan, J., Borland, R., Cosolo, W., Millership, R., Haines, I., Zimet, A., and Zalcborg, J. Patients' beliefs about cancer management. *Supportive Care in Cancer* 4[2], 110-117. 1996.

Excl reason: Not in PICO

Cagle, J. G. and Kovacs, P. J. Education: a complex and empowering social work intervention at the end of life. *Health & Social Work* 34[1], 17-27. 2009.

Excl reason: Not in PICO

Cairns, D., Thomas, L., Mooney, V., and Pace, J. B. A comprehensive treatment approach to chronic low back pain. *Pain* 2[3], 301-308. 1976.

Excl reason: Not in PICO

Capewell, C., Gregory, W., Closs, S., and Bennett, M. Brief DVD-based educational intervention for patients with cancer pain: feasibility study. *Palliative Medicine* 24[6], 616-622. 2010.

Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Patient information material. 1 patient's questions w/ answer from from doctor

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Narrative review

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Excl reason: Not in PICO

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Excl reason: Not in PICO

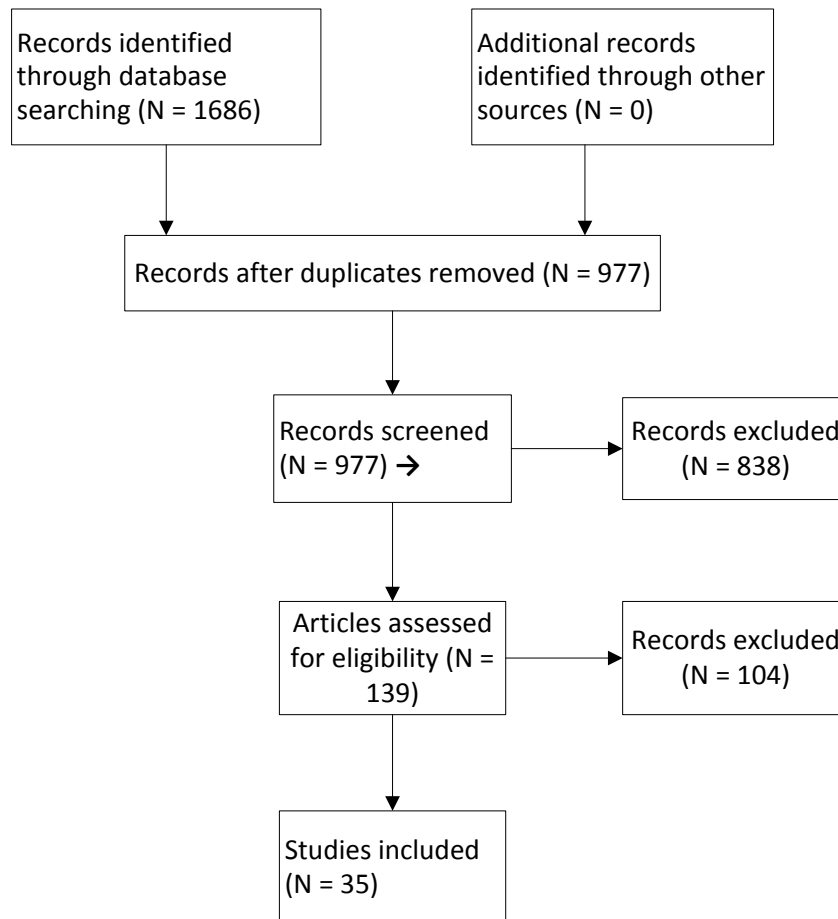
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Excl reason: Not in PICO

Flow diagram of excluded studies for review Question 2

What is the most effective first-line opioid treatment in patients with advanced and progressive disease who require strong opioids?



Excluded studies:

Transdermal fentanyl (new preparation). Helpful alternative to morphine and to oral and subcutaneous routes. Prescrire International 7[37], 137-140. 1998.

Excl reason: Not in PICO

Oral transmucosal fentanyl: new preparation. For breakthrough cancer pain when morphine fails. Prescrire International 11[60], 106-107. 2002.

Excl reason: Narrative review

Oral oxycodone: new preparation. No better than oral morphine. Prescrire International 12[65], 83-84. 2003.

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Excl reason: Not in PICO

Fentanyl sublingual tablet: A guide to its use in breakthrough pain in opioid-tolerant adults with cancer. Drugs and Therapy Perspectives 27[7], 6-9. 2011.

Excl reason: Not RCT

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Duplicate

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Excl reason: Population not in PICO

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Excl reason: Duplicate

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Excl reason: Not RCT

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Excl reason: Population and comparison not in PICO

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Excl reason: Not RCT

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Excl reason: Not RCT

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Excl reason: Same as Ahmedzai 1997? Abstract

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Excl reason: Included in Caraceni et al. (2010) and in Tassinari et al. (2008) 2B

Ahmedzai, S., Brooks, D., Ahmedzai, S., and Brooks, D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *Journal of Pain & Symptom Management* 13[5], 254-261. 1997.

Excl reason: Duplicate

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Duplicate

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Excl reason: Narrative review

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Excl reason: Duplicate

Apolone, G., Corli, O., Negri, E., Mangano, S., Montanari, M., Greco, M. T., Cancer Pain Outcome Research Study Group (, Apolone, G., Bertetto, O., Caraceni, A., Corli, O., De, Conno F., Labianca, R., Maltoni, M., Nicora, Maria F., Torri, V., Zucco, F., Apolone, Giovanni, Corli, Oscar, Negri, Emanuele, Mangano, Simone, Montanari, Mauro, Bertetto, Maria Teresa, Cancer Pain Outcome Research Study Group (, Apolone, Giovanni, Bertetto, Oscar, Caraceni, Augusto, Corli, Oscar, De Conno, Franco, Labianca, Roberto, Maltoni, Marco, Nicora Maria, Flavia, Torri, Valter, and Zucco, Furio. Effects of transdermal buprenorphine on patients-reported outcomes in cancer patients: results from the Cancer Pain Outcome Research (CPOR) Study Group. *Clinical Journal of Pain* 25[8], 671-682. 2009.

Excl reason: Not RCT

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Excl reason: Narrative review

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Excl reason: Duplicate

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Excl reason: Duplicate

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Excl reason: Duplicate

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Excl reason: Not in PICO: Morphine v morphine (dose differences)

Portenoy, R. K., Payne, R., Coluzzi, P., Raschko, J. W., Lyss, A., Busch, M. A., Frigerio, V., Ingham, J., Loseth, D. B., Nordbrock, E., and Rhiner, M. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. SO: Pain 79[2-3], 303-312. 1999.

Excl reason: In Cochrane review: Fentanyl v fentanyl

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Excl reason: Not in PICO: fentanyl buccal tablet v placebo

Portenoy, R. K., Farrar, J. T., Backonja, M. M., Cleeland, C. S., Yang, K., Friedman, M., Colucci, S. V., Richards, P., Portenoy, Russell K., Farrar, John T., Backonja, Misha Miroslav, Cleeland, Charles S., Yang, Kaity, Friedman, Michael, Colucci, Salvatore V., and Richards, Patricia. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clinical Journal of Pain 23[4], 287-299. 2007.
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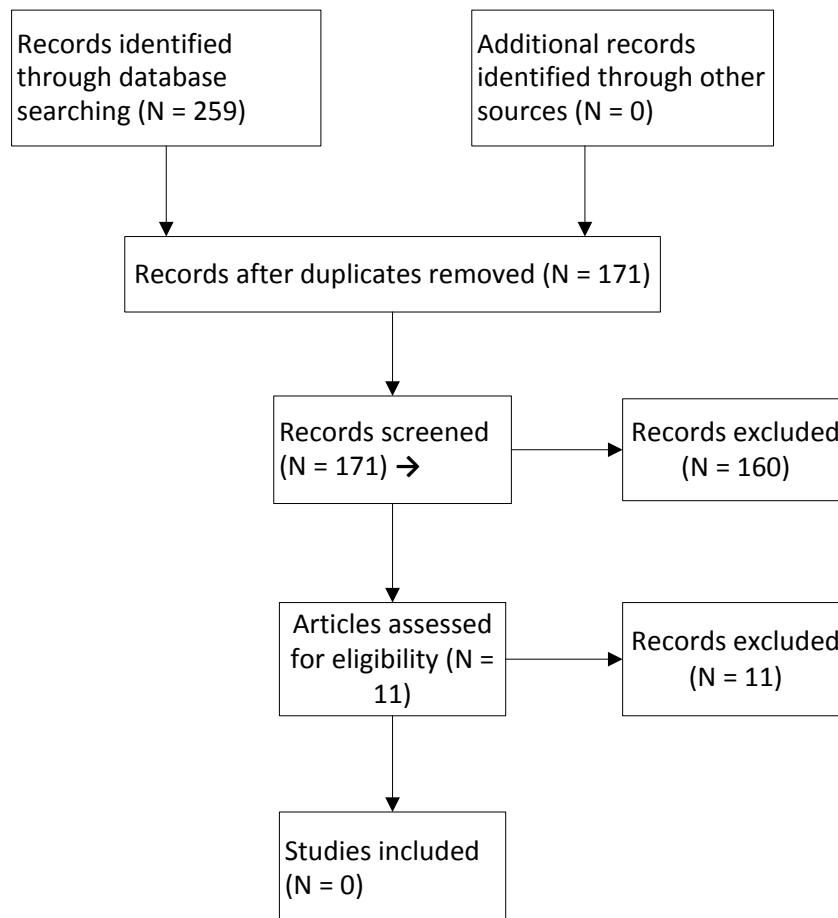
Excl reason: Not in PICO

Zuurmond, W. W. Safety and efficacy of transdermal fentanyl (Durogesic) compared with sustained-release morphine in patients with cancer pain [abstract]. *SO: Proceedings of the American Society of Clinical Oncology* 21 (Pt 1), 377a, Abstract. 2002.

Excl reason: Duplicate

Flow diagram of excluded studies for review Question 3

What is the most effective management of side effects of strong opioids?



Excluded studies

Methylnaltrexone: A guide to its use in opioid-induced constipation in patients with advanced illness. *Drugs and Therapy Perspectives* 26[12], 5-8. 2010.

Excl reason: Not in PICO

Agra Varela, Y. A. S. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *Journal of Pain and Symptom Management* 15[1], 1-7. 1998.

Excl reason: Not in PICO

Agra, Y., Sacristan, A., Gonzalez, M., Ferrari, M., Portugues, A., Calvo, M. J., Agra, Y., Sacristan, A., Gonzalez, M., Ferrari, M., Portugues, A., and Calvo, M. J. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *Journal of Pain & Symptom Management* 15[1], 1-7. 1998.

Excl reason: Duplicate

Barrow, P. M., Hughes, D. G., Redfern, N., and Urie, J. Influence of Droperidol on Nausea and Vomiting During Patient-Controlled Analgesia. *British Journal of Anaesthesia* 72[4], 460-461. 1994.

Excl reason: Not in PICO

Becker, G., Galandi, D., and Blum, H. E. Peripherally Acting Opioid Antagonists in the Treatment of Opiate-Related Constipation: A Systematic Review. *Journal of Pain and*

Symptom Management 34[5], 547-565. 2007.
Excl reason: Not in PICO

Bennett, M. Factors influencing constipation in advanced cancer patients: A prospective study of opioid dose, dantrolene dose and physical functioning. *Palliative Medicine* 17[5], 418-422. 2003.
Excl reason: Not in PICO/Not RCT

Benyamin, R. Opioid complications and side effects. *Pain Physician* 11[SPEC. ISS. 2], S105-S120. 2008.
Excl reason: Narrative review

Bignell, M. Naloxone hydrochloride sr gastro-resistant sustained release capsules, (Nalcol) as a treatment for functional constipation: A randomised, double blind controlled trial in secondary care - Preliminary results. *Gastroenterology Conference*[var.pagings], S614. 2011.
Excl reason: Not in PICO

Binsfeld, H., Szczepanski, L., Waechter, S., Richarz, U., Sabatowski, R., Binsfeld, Heinrich, Szczepanski, Leszek, Waechter, Sandra, Richarz, Ute, and Sabatowski, Rainer. A randomized study to demonstrate noninferiority of once-daily OROS([REGISTERED]) hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain. *Pain Practice* 10[5], 404-415. 2010.
Excl reason: Not in PICO

Blonsky, R. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic non-malignant pain. *Journal of Pain Conference*[var.pagings], S52. 2009.
Excl reason: Not in PICO

Bradshaw, M. and Sen, A. Use of a prophylactic antiemetic with morphine in acute pain: randomised controlled trial. *SO: Emergency medicine journal : EMJ* 23[3], 210-213. 2006.
Excl reason: Not in PICO

Bruera, E., Belzile, M., Neumann, C., Harsanyi, Z., Babul, N., and Darke, A. A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. *Journal of Pain and Symptom Management* 19[6], 427-435. 2000.
Excl reason: Not in PICO

Candy, B. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane database of systematic reviews (Online)* 1[pp CD003448], 2011. 2011.
Excl reason: SR, but no data synthesis. Analyses not in PICO.

Chamberlain, B. Laxative use in patients with advanced illness and opioid-induced constipation treated with subcutaneous methylnaltrexone. *Palliative Medicine Conference*[var.pagings], S129. 2010.
Excl reason: Not in PICO

Chamberlain, B. H., Cross, K., Winston, J. L., Thomas, J., Wang, W., Su, C., Israel, R. J., Chamberlain, Bruce H., Cross, Karen, Winston, Jaron L., Thomas, Jay, Wang, Wenjin, Su, Chinyu, and Israel, Robert J. Methylnaltrexone treatment of opioid-induced constipation in patients with advanced illness. *Journal of Pain & Symptom Management* 38[5], 683-690. 2009.
Excl reason: Not in PICO

Chan, S. L. Serotonin antagonists for the treatment of opioid-induced nausea and vomiting in non-surgical patients (Structured abstract). *SO: Singapore General Hospital Proceedings* 18[1], 33-38. 2009.
Excl reason: (Analyses) not in PICO

Chang, A. K. B. Efficacy and safety profile of a single dose of hydromorphone compared with morphine in older adults with acute, severe pain: A prospective, randomized, double-blind clinical trial. *American Journal Geriatric Pharmacotherapy* 7[1], 1-10. 2009.

Excl reason: Not in PICO

Chen, T. Y. and Rosow, C. E. Methylnaltrexone bromide. *Drugs of the Future* 32[9], 771-775. 2007.

Excl reason: Not in PICO

Cherasse, A., Muller, G., Ornetti, P., Piroth, C., Tavernier, C., Maillefert, J. F., Cherasse, Anne, Muller, Geraldine, Ornetti, Paul, Piroth, Christine, Tavernier, Christian, and Maillefert, Jean Francis. Tolerability of opioids in patients with acute pain due to nonmalignant musculoskeletal disease. A hospital-based observational study. *Joint, Bone, Spine: Revue du Rhumatisme* 71[6], 572-576. 2004.

Excl reason: Not RCT

Cherny, Nathan, Ripamonti, Carla, Pereira, Jose, Davis, Carol, Fallon, Marie, McQuay, Henry, Mercadante, Sebastiano, Pasternak, Gavrill, and Ventafridda, Vittorio. Strategies to Manage the Adverse Effects of Oral Morphine: An Evidence-Based Report. *Journal of Clinical Oncology* 19[9], 2542-2554. 1-5-2001.

Excl reason: Narrative review/expert opinion

Clark, A. J., Ahmedzai, S. H., Allan, L. G., Camacho, F., Horbay, G. L., Richarz, U., Simpson, K., Clark, A. J., Ahmedzai, S. H., Allan, L. G., Camacho, F., Horbay, G. L. A., Richarz, U., and Simpson, K. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. *Current Medical Research & Opinion* 20[9], 1419-1428. 2004.

Excl reason: Not in PICO for topic 2, but SR? TOPIC1?

Clemens, K. E., Quednau, I., and Klaschik, E. Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets in patients with advanced cancer. *International Journal of Clinical Practice* 65[4], 472-478. 2011.

Excl reason: Not in PICO/Not RCT

Clemens, K. E. K. Managing opioid-induced constipation in advanced illness: Focus on methylnaltrexone bromide. *Therapeutics and Clinical Risk Management* 6[1], 77-82. 2010.

Excl reason: Narrative review

Clemens, K. E. M. Combined oral prolonged-release oxycodone and naloxone in opioid-induced bowel dysfunction: Review of efficacy and safety data in the treatment of patients experiencing chronic pain. *Expert Opinion on Pharmacotherapy* 11[2], 297-310. 2010.

Excl reason: Not in PICO

Crownover, B. Methylnaltrexone (Relistor) for opioid-induced constipation. *American Family Physician* 82[6]. 2010.

Excl reason: Not in PICO

Cryer, B. L. K. A phase 3, randomized, double-blind, placebo-controlled clinical trial of lubiprostone for the treatment of opioid-induced bowel dysfunction in patients with chronic, non-cancer pain. *Gastroenterology Conference*[var.pagings], S129. 2010.

Excl reason: Not in PICO

Cubero, D. I. G. Early switching from morphine to methadone is not improved by acetaminophen in the analgesia of oncologic patients: A prospective, randomized, double-blind, placebo-controlled study. *Supportive Care in Cancer* 18[2], 235-242. 2010.

Excl reason: Not in PICO (acetaminophen = paracetamol)

Culebras. The antiemetic efficacy of droperidol added to morphine patient-controlled analgesia: A randomized, controlled, multicenter dose-finding study (vol 97, pg 816, 2003).

Anesthesia and Analgesia 98[1], 88. 2004.
Excl reason: Not in PICO

Davis, M. P. H. A Systematic Review of the Treatment of Nausea and/or Vomiting in Cancer Unrelated to Chemotherapy or Radiation. Journal of Pain and Symptom Management 39[4], 756-767. 2010.
Excl reason: Not in PICO

Deibert, P., Xander, C., Blum, H. E., Becker, G., Deibert, Peter, Xander, Carola, Blum, Hubert E., and Becker, Gerhild. Methylnaltrexone: the evidence for its use in the management of opioid-induced constipation. Core Evidence 4, 247-258. 2010.
Excl reason: Not in PICO

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Excl reason: Not in PICO

Diego, L. Methylnaltrexone: A novel approach for the management of opioid-induced constipation in patients with advanced illness. Expert Review of Gastroenterology and Hepatology 3[5], 473-485. 2009.
Excl reason: Not in PICO

DiPetrillo, L. ALKS 37, A novel, peripherally-restricted opioid receptor antagonist, demonstrates efficacy in the treatment of opioid-induced bowel dysfunction. Gastroenterology Conference[*var.pagings*], S136. 2011.
Excl reason: Not in PICO

Duerden, M. Subcutaneous methylnaltrexone improves bowel movement frequency and quality in patients with chronic non-malignant pain and opioid induced constipation. Journal of Pain Conference[*var.pagings*], S46. 2010.
Excl reason: Not in PICO

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Excl reason: Not in PICO

Dy, S. M. and Apostol, C. C. Evidence-based approaches to other symptoms in advanced cancer. Cancer Journal from Scientific American 16[5], 507-513. 2010.
Excl reason: Not in PICO

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Excl reason: Not in PICO

Eisenberg E. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and meta-analysis of randomized controlled trials. Journal of the American Medical Association 293[24], 3043-3052. 2005.
Excl reason: Not in PICO

Fleming, V. A review of laxative therapies for treatment of chronic constipation in older adults. American Journal Geriatric Pharmacotherapy 8[6], 514-550. 2010.
Excl reason: Not in PICO

Foss, J. How safe and effective is methylnaltrexone for the treatment of opioid-induced constipation in advanced illness? Nature Clinical Practice Gastroenterology & Hepatology 6[1], 12-13. 2009.
Excl reason: Not in PICO

Foss, J. F. A review of the potential role of methylnaltrexone in opioid bowel dysfunction. *American Journal of Surgery* 182[5A], 19S-26S. 2001.
Excl reason: Not in PICO

Fredheim, O. M. S. Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: A nine-month follow-up study. *Palliative Medicine* 20[1], 35-41. 2006.
Excl reason: Not in PICO

Freedman, M. D. S. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: A double-blinded placebo-controlled trial. *Journal of Clinical Pharmacology* 37[10], 904-907. 1997.
Excl reason: Population not in PICO

Friedman, J. D. D. Opioid antagonists in the treatment of opioid-induced constipation and pruritus. *Annals of Pharmacotherapy* 35[1], 85-91. 2001.
Excl reason: Not in PICO

Galvin, E., Boesjes, H., Hol, J., Ubben, J. F., Klein, J., Verbrugge, S. J., Galvin, E., Boesjes, H., Hol, J., Ubben, J. F., Klein, J., and Verbrugge, S. J. C. Modafinil reduces patient-reported tiredness after sedation/analgesia but does not improve patient psychomotor skills. *Acta Anaesthesiologica Scandinavica* 54[2], 154-161. 2010.
Excl reason: Not in PICO

Garnock-Jones, K. P. M. Methylnaltrexone. *Drugs* 70[7], 919-928. 2010.
Excl reason: Not in PICO

Goodarzi, M. and Goodarzi, M. Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. *Paediatric Anaesthesia* 9[5], 419-422. 1999.
Excl reason: Not in PICO

Greenwald, P. W. P. Low-dose naloxone does not improve morphine-induced nausea, vomiting, or pruritus. *American Journal of Emergency Medicine* 23[1], 35-39. 2005.
Excl reason: Not in PICO

Hardy, J., Daly, S., McQuade, B., Albertsson, M., Chimontsi, Kypriou, V., Stathopoulos, P., and Curtis, P. A double-blind, randomised, parallel group, multinational, multicentre study comparing a single dose of ondansetron 24 mg p.o. with placebo and metoclopramide 10 mg t.d.s. p.o. in the treatment of opioid-induced nausea and emesis in cancer patients. *Supportive Care in Cancer* 10[3], 231-236. 2002.
Excl reason: Comparison not in PICO

Hawley, P. H. and Byeon, J. J. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *Journal of Palliative Medicine* 11[4], 575-581. 2008.
Excl reason: Not in PICO (laxative v laxative)/Not RCT

Healy, R. Effectiveness of two opioid antagonists in treating opioid-induced constipation. *British journal of nursing* (Mark Allen Publishing) 18[16], 998-1002. 2009.
Excl reason: Not in PICO

Herndon, C. M., Jackson, K. C., and Hallin, P. A. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. *Pharmacotherapy* 22[2], 240-250. 2002.
Excl reason: Narrative review

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Excl reason: Narrative review

Holzer, P. Opioid antagonists for prevention and treatment of opioid-induced gastrointestinal effects. *Current Opinion in Anaesthesiology* 23[5], 616-622. 2010.

Excl reason: Not in PICO

Ilias, W. Patient-controlled analgesia in chronic pain patients: Experience with a new device designed to be used with implanted programable pumps. *Pain Practice* 8[3], 164-170. 2008.

Excl reason: Not in PICO/Not RCT

Irving, G., Penzes, J., Ramjattan, B., Cousins, M., Rauck, R., Spierings, E. L., Kleoudis, C. S., Snidow, J. W., Pierce, A., Wurzelmann, J., Mortensen, E. R., Irving, Gordon, Penzes, Janos, Ramjattan, Brian, Cousins, Michael, Rauck, Richard, Spierings, Egilius L. H., Kleoudis, Christi S., Snidow, Jerry W., Pierce, Amy, Wurzelmann, John, and Mortensen, Eric R. A randomized, placebo-controlled phase 3 trial (study SB-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *Journal of Pain* 12[2], 175-184. 2011.

Excl reason: Not in PICO

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Excl reason: Not in PICO

Iyer S. Effect of subcutaneous (SC) methylnaltrexone on generic health related quality of life using the eq-5d index scores in patients with chronic non-malignant pain and opioid-induced constipation. *Value in Health Conference[var.pagings]*, A348-A349. 2009.

Excl reason: Not in PICO

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Excl reason: Not in PICO

Johnson, D. A. Treating chronic constipation: How should we interpret the recommendations? *Clinical Drug Investigation* 26[10], 547-557. 2006.

Excl reason: Not in PICO

Koetter, Kai and Kranke, Peter. Prevention and treatment interventions for nausea and vomiting during initiation of chronic opioid therapy. SO: Koetter Kai, Kranke Peter. Prevention and treatment interventions for nausea and vomiting during initiation of chronic opioid therapy. *Cochrane Database of Systematic Reviews: Protocols* 2008 [1]. 2008. John Wiley & Sons, Ltd.

Excl reason: Protocol

Kreek, M. J., Schaefer, R. A., Hahn, E. F., Fishman, J., Kreek, M. J., Schaefer, R. A., Hahn, E. F., and Fishman, J. Naloxone, a specific opioid antagonist, reverses chronic idiopathic constipation. *Lancet* 1[8319], 261-262. 5-2-1983.

Excl reason: Not in PICO

Kress, H. G., Von der, Laage D., Hoerauf, K. H., Nolte, T., Heiskanen, T., Petersen, R., Lundorff, L., Sabatowski, R., Krenn, H., Rosland, J. H., Saedder, E. A., Jensen, N. H., Kress, Hans G., Von der Laage, Dorothea, Hoerauf, Klaus H., Nolte, Thomas, Heiskanen, Tarja, Petersen, Rasmus, Lundorff, Lena, Sabatowski, Rainer, Krenn, Herbert, Rosland, Jan H., Saedder, Eva A., and Jensen, Niels Henrik. A randomized, open, parallel group, multicenter trial to investigate analgesic efficacy and safety of a new transdermal fentanyl patch compared to standard opioid treatment in cancer pain. *Journal of Pain & Symptom Management* 36[3], 268-279. 2008.

Excl reason: Not in PICO

Kurz, A. Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. *Drugs* 63[7], 649-671. 2003.
Excl reason: Narrative review

Lal, L. S., X. Economic analysis of the potential usages of alvimopan and methylnaltrexone at a tertiary cancer center. *Value in Health Conference[var.pagings]*, A59. 2009.
Excl reason: Not in PICO

Latasch, L., Zimmermann, M., Eberhardt, B., Jurna, I., Latasch, L., Zimmermann, M., Eberhardt, B., and Jurna, I. [Treatment of morphine-induced constipation with oral naloxone]. [German]. *Anaesthesist* 46[3], 191-194. 1997.
Excl reason: Not in PICO

Latasch, L., Zimmermann, M., Eberhardt, B., and Jurna, I. Oral naloxone antagonizes morphine-induced constipation. *Anaesthesist* 46[3], 191-194. 1997.
Excl reason: Not in PICO

Laugsand, E. A. K. Management of opioid-induced nausea and vomiting in cancer patients: Systematic review and evidence-based recommendations. *Palliative Medicine* 25[5], 442-453. 2011.
Excl reason: SR, but not in PICO (and no data synthesis)

Laval, G. Symptomatic treatments (pain management excluded) for adults in palliative care. *Revue du Praticien* 59[6], 785-797. 2009.
Excl reason: Not in PICO

Lee, Y. Lai. A Dose Ranging Study of Dexamethasone for Preventing Patient-Controlled Analgesia-Related Nausea and Vomiting: A Comparison of Droperidol with Saline. *Anesthesia and Analgesia* 98[4], 1066-1071. 2004.
Excl reason: Not in PICO

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Excl reason: Not in PICO

Leppert, W. Role of oxycodone and oxycodone/naloxone in cancer pain management. *Pharmacological Reports* 62[4], 578-591. 2010.
Excl reason: Narrative review

Leppert, W. The role of opioid receptor antagonists in the treatment of opioid-induced constipation: A review. *Advances in Therapy* 27[10], 714-730. 2010.
Excl reason: Not in PICO

Licup, N. and Baumrucker, S. J. Methylnaltrexone: Treatment for Opioid-Induced Constipation. *American Journal of Hospice & Palliative Medicine* 28[1], 59-61. 2011.
Excl reason: Not in PICO

Lipman, A. G., Karver, S., Austin, Cooney G., Stambler, N., Israel, R. J., Lipman, Arthur G., Karver, Sloan, Austin Cooney, Gail, Stambler, Nancy, and Israel, Robert J. Methylnaltrexone for opioid-induced constipation in patients with advanced illness: a 3-month open-label treatment extension study. *Journal of Pain & Palliative Care Pharmacotherapy* 25[2], 136-145. 2011.
Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

Lundorff, L. E., Jonsson, B. H., Sjogren, P., Lundorff, L. E., Jonsson, B. H., and Sjogren, P. Modafinil for attentional and psychomotor dysfunction in advanced cancer: a double-blind, randomised, cross-over trial. *Palliative Medicine* 23[8], 731-738. 2009.

Excl reason: Not in PICO

Mancini, I. and Bruera, E. Constipation in advanced cancer patients. *Supportive Care in Cancer* 6[4], 356-364. 1998.

Excl reason: Narrative review

Mantovani, G., Curreli, L., Maccio, A., Massa, E., Massa, D., Mulas, C., Succu, G., and Contu, P. Prevention of nausea and vomiting (N and V) in cancer patients receiving high-dose cisplatin. Assessment of the potential antiemetic activity of transdermal fentanyl (TTS-F) compared to standard antiemetic treatment in acute and delayed N and V: First clinical report. *Anticancer Research* 19[4 C], 3495-3502. 1999.

Excl reason: Not in PICO

Marcushamer, M. Reduced promethazine dose with meperidine: antiemetic effect. (Research Abstract). *SO: Pediatr-Dent* 18[2]. 1996.

Excl reason: Not in PICO

Masri, Y., Abubaker, J., and Ahmed, R. Prophylactic use of laxative for constipation in critically ill patients. *Annals of Thoracic Medicine* 5[4], 228-231. 2010.

Excl reason: Not in PICO

McNamara, P. Opioid switching from morphine to transdermal fentanyl for toxicity reduction in palliative care. *Palliative Medicine* 16[5], 425-434. 2002.

Excl reason: Not RCT

McNamara, P. and McNamara, Paul. Opioid switching from morphine to transdermal fentanyl for toxicity reduction in palliative care. *Palliative Medicine* 16[5], 425-434. 2002.

Excl reason: Not RCT

McNicol E. Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. *Journal of Pain* 4[5], 231-256. 2003.

Excl reason: SR (of all study types), but with no data synthesis

Meissner, W., Schmidt, U., Hartmann, M., Kath, R., Reinhart, K., Meissner, W., Schmidt, U., Hartmann, M., Kath, R., and Reinhart, K. Oral naloxone reverses opioid-associated constipation. *Pain* 84[1], 105-109. 2000.

Excl reason: Not in PICO

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Excl reason: (Comparison) Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not RCT

Mercadante, S., Villari, P., Ferrera, P., Casuccio, A., Mercadante, Sebastiano, Villari, Patrizia, Ferrera, Patrizia, and Casuccio, Alessandra. Opioid-induced or pain relief-reduced symptoms in advanced cancer patients? *European Journal of Pain: Ejp* 10[2], 153-159. 2006.

Excl reason: Not RCT

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Excl reason: Not in PICO/Not RCT

Michna E. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain. *Anaesthesia and Intensive Care Conference*[var.pagings], 586. 2010.

Excl reason: Not in PICO

Mihaylov, S., Stark, C., McColl, E., Steen, N., Vanoli, A., Rubin, G., Curless, R., Barton, R., Bond, J., Mihaylov, S., Stark, C., McColl, E., Steen, N., Vanoli, A., Rubin, G., Curless, R., Barton, R., and Bond, J. Stepped treatment of older adults on laxatives. The STOOL trial. *Health Technology Assessment (Winchester, England)* 12[13], iii-139. 2008.

Excl reason: Not in PICO

Miles, C. L. F. Laxatives for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews* [4]. 2006.

Excl reason: Not in PICO

Miyazaki, T., Hanaoka, K., Namiki, A., Ogawa, S., Kitajima, T., Hosokawa, T., Ishida, T., Nogami, S., Mashimo, S., Miyazaki, Toyo, Hanaoka, Kazuo, Namiki, Akiyoshi, Ogawa, Setsuro, Kitajima, Toshimitsu, Hosokawa, Toyoshi, Ishida, Tomozo, Nogami, Shoji, and Mashimo, Shigeto. Efficacy, safety and pharmacokinetic study of a novel fentanyl-containing matrix transdermal patch system in Japanese patients with cancer pain. *Clinical Drug Investigation* 28[5], 313-325. 2008.

Excl reason: Not in PICO

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Opioids in palliative care:
safe and effective prescribing of strong
opioids for pain in palliative care of
adults

Appendix E – Evidence tables

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3.1 Communication

Review question 1: What information do patients with advanced and progressive disease who require strong opioids, or their carers, need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid?

Evidence table 1

<p>Citation: Bender, J. L., Hohenadel, J., Wong, J., Katz, J., Ferris, L. E., Shobbrook, C., Warr, D., and Jadad, A. R. What Patients with Cancer Want to Know About Pain: A Qualitative Study. <i>Journal of Pain and Symptom Management</i> 35[2], 177-187. 2008.</p>
<p>Design: Qualitative study Country: Canada Aim: To explore what patients with breast cancer want to know about pain.</p>
<p>Inclusion criteria Patients with pain (of any kind and severity) associated with breast cancer or its treatment, ≥ 18 years old, and who were able to understand spoken and written English. Recruitment was stopped when data saturation was reached.</p>
<p>Exclusion criteria None listed</p>
<p>Population An opportunity sample of N = 18 patients with breast cancer recruited from the breast cancer and pain clinics from June to October 2003: N = 14 were > 55 years old; years since diagnosis: 0-5 (N = 8), 6-10 (N = 5), 11+ (N = 5); N = 10 had metastatic breast cancer; treatments received: Surgery (N = 17), radiation therapy (N = 12), chemotherapy (N = 14); N = 9 had > 1 pain; pain intensity at its worst (measured on 4-point verbal scale [none, mild moderate, severe]): Mild (N = 2), severe (N = 16); pain intensity in the last 7 days: Mild (N = 10), moderate (N = 6), severe (N = 2); pain intensity at the interview: None (N = 1), mild (N = 13), moderate (N = 2), severe (N = 2); current analgesic therapy: None (N = 2), NSAIDs or acetaminophen (N = 3), opioid (N = 13); attributed cause of pain: Cancer (N = 8), treatment (N = 7), unknown (N = 2), unrelated (N = 1).</p>
<p>Interventions 60-minute (approximately), audio-recorded semi-structured interviews were conducted by one person either following a scheduled clinic appointment or by telephone. Open-ended questions were used to guide the interview. Participants were asked about their experiences with pain, related questions and concerns, specific information they wished they knew more about or had known earlier, questions they asked their health professionals, and any unanswered questions. Clarification probes and follow-up questions were used to clarify and explore issues in greater depth and to verify our understanding of the information being collected. <i>Only the result relevant to the clinical question will be reported.</i></p>
<p>Outcomes See Results section.</p>
<p>Results - The patients expressed a desire to know all options for pain control available, how the drugs or treatments work, expected side effects, and under what circumstances they are used to treat pain. Many described a period of time when they endured severe pain because they were not aware of the treatment options available. - Several practical questions about the use and administration of analgesic medication were raised, including when and how the medication should be taken, how often, for how long, when to expect pain relief, and the expected duration of the relief. Concerns about addiction and tolerance were common, particularly with respect to the use of opioids. Fear of unpleasant or unmanageable side effects prompted many to avoid or discontinue pain medication. - “‘How long before it starts working?’ ‘How long it’s going to work for?’ ‘If I’m taking my pill at 8:00 in the morning, ‘when should I feel relief?’ ‘An hour later, twenty minutes later?’ And if I’m taking them every twelve hours, ‘Is it going to last the twelve hours?’”[Participant 18]</p>
<p>General comments This qualitative study appears to have been conducted to a high quality using solid qualitative study methodology, including pilot testing of the interview guide to ensure the clarity of the questions and follow-up probes, on-going development and integration of new questions in successive interviews as new issues and themes emerged, and independent coding of the majority of the transcripts by more than one researcher. However, the population and main aims of the study do not exactly match those of the clinical question, although the majority of the patients were receiving opioid</p>

treatment, therefore the data provided by this study is very limited in this context.
References of Included Studies (For systematic reviews): N/A
<p>Citation: Blanchard, H. and Batten, B. Designing and producing a patient leaflet on morphine. <i>European Journal of Palliative Care</i> 3[3], 106-108. 1996.</p> <p>Design: Qualitative study Country: United Kingdom Aim: To investigate cancer patients' knowledge of morphine.</p> <p>Inclusion criteria Patients with terminal cancer.</p> <p>Exclusion criteria Patients who were confused, too ill to participate (mentally or physically) or who declined.</p> <p>Population N = 47 patients, 31/47 patients were taking or had previously taken morphine and 16/47 patients were not taking morphine.</p> <p>Interventions 15-minute interviews were conducted by one person over a 3-week period. Patients were individually interviewed at several UK locations and settings (inpatients, day-care unit, oncology outpatients, hospice and at home). The interviews were carried out according to the following format: 1) An open question, giving the patient an opportunity to ask questions or express concerns about morphine 2) Structured questions on knowledge about morphine. <i>The result of these are not relevant to the clinical question so will not be reported.</i></p> <p>Outcomes See Results section.</p> <p>Results 17/31 patients taking or having previously taken morphine provided responses to the open question. The most common concerns or questions were: - Will I become addicted? (8) - What are the side-effects? (8, including more specific questions, for example about constipation) - Am I near the end? (4) - Can I drink alcohol? (2) 7/16 patients not on morphine volunteered the following potential questions/concerns: - Am I 'near the end'? - Is it a poison? - What are the side-effects?</p> <p>General comments This short paper provides so little detail about the methods employed and the results that it is not possible to properly appraise the study comprehensively.</p> <p>References of Included Studies (For systematic reviews): N/A</p>

<p>Citation: Reid, C. M., Gooberman-Hill, R., and Hanks, G. W. Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. <i>Annals of Oncology</i> 19[1], 44-48. 2008.</p> <p>Design: Qualitative Country: United Kingdom Aim: To explore the factors influencing the decision to accept/reject morphine when first offered to patients with cancer.</p> <p>Inclusion criteria Participants were recruited from a pain management trial that took place in a UK oncology centre. Patients who had uncontrolled pain caused by cancer and were only taking paracetamol or a nonsteroidal anti-inflammatory drug for pain were eligible for the trial. On entering, they were randomized to either the traditional World Health Organization three-step analgesic ladder and prescribed a step II analgesic (cocodamol) or to an experimental two-step approach and prescribed a step III opioid (oxycodone). Participants were informed that if they agreed to take part, they had a 50/50</p>

chance of being allocated to oxycodone, described in the patient information sheet as being similar to ‘morphine’. All patients who both entered and declined participation in the trial were approached to request an interview.
Exclusion criteria None listed
<p>Population</p> <p>- N = 29 were approached about the interview study and 18 took part. Of these 18, 12 had also agreed to participate in the two-step trial. 5 patients who entered the two-step trial did not participate because they died soon after study entry. 6 other patients were approached about the interviews but did not take part (N = 2 died very quickly, N = 4 did not want to take part).</p> <p>- N = 18 patients: Age range: 55- 82 years, all white, 9 women. All participants described how pain had a significant impact on their lives, often resulting in loss of mobility, function or role. N = 10 had recently had news of disease spread. Analgesics at time of interview: Oxycodone (N = 5), regular cocodamol plus ‘as required’ morphine (N = 2), regular modified-release morphine (N = 2), regular normal-release morphine (N = 1), paracetamol (N = 1), paracetamol plus ‘as required’ morphine (N = 2), cocodamol (N = 2), ibuprofen ‘as required’ (N = 1), morphine ‘as required’ (N = 1), nil (n = 1).</p>
<p>Interventions</p> <p>The majority of the participants were interviewed in their own homes by one of the authors and most took place within 2 weeks of their trial recruitment interview. The interviews were conducted with the aid of a topic guide and participants were asked to describe their pain and its impact upon their lives, their recollections of the consultation when the trial was discussed, their associations with morphine, the flexibility of their decision to commence or delay opioids and the influence of others upon that decision. Interviews were audio-recorded, transcribed verbatim and anonymised. <i>Only the result relevant to the clinical question will be reported.</i></p>
Outcomes See Results section.
<p>Results</p> <p>- The professional was mentioned often during the interviews. Participants described the way in which professionals had communicated about pain, how opioids were offered (in particular whether or not they were offered as choice), and discussed trust in their professional.</p> <p>- Participants preferred unhurried consultations in which pain was seen as important. Some did not expect their pain to be addressed during oncology clinics because they perceived the staff to already have high workloads.</p> <p>- The manner in which the professionals communicated about opioids was important. Participants felt more able to accept inclusion in the pain management trial when they were told that opioids were being commenced at a ‘low dose’ and opioids could be discontinued if side-effects developed.</p> <p>- Participants appreciated professionals who spoke about opioids with knowledge and confidence but were sometimes suspicious about the idea of ‘choice’: “They actually don’t say, “Mr Smith, would you like to take the morphine?” They always say, “It’s your choice.”.. If it is my choice, what are they not telling me?” Harvey</p> <p>- Half of the participants mentioned trust in the professional as an important factor in their decision to take opioids. For some, trusting the professional allowed them to make their own decision to commence, whereas for others, trust meant that they could allow that the professional to make the decision on their behalf: “No, no I’d think to myself, “Well they’re putting me onto something else which is a stronger drug to help me.”.. And I just accepted that. I mean when I go to any doctor—well most doctors anyway—.. I always go in there with the idea that they know what they’re doing.” Jim</p>
<p>General comments</p> <p>This qualitative study appears to have been conducted to a high quality using solid qualitative study methodology, including ensuring data saturation, independent data coding by more than one researcher, and negative case analysis. However, the main aims of the study do not exactly match those of the clinical question therefore the data provided by this study is very limited in this context.</p>
References of Included Studies (For systematic reviews): N/A

3.3 Starting strong opioids – titrating the dose with immediate-release, sustained-release or transdermal patches

Review question 2: What is the most effective first-line opioid treatment in patients with advanced and progressive disease who require strong opioids?

2a: Are immediate-release opioids (morphine/oxycodone) more effective than sustained-release opioids (morphine/oxycodone) or opioid patches (fentanyl/buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?

Evidence table 2

Citation: Arkinstall, W. W., Goughnour, B. R., White, J. A., Stewart, J. H., Arkinstall, W. W., Goughnour, B. R. et al. (1989). Control of severe pain with sustained-release morphine tablets v. oral morphine solution. <i>CMAJ Canadian Medical Association Journal</i> , 140, 653-657.		
Design: Randomised, double-blind/double dummy cross-over study Country: Canada Aim: To compare the efficacy of sustained-release (SR) morphine sulphate tablets given every 12 hours to morphine sulphate solution given every 4 hours		
Inclusion criteria <ul style="list-style-type: none"> • Age \geq 19 years • Analgesic regimen \geq 60mg/day of orally given morphine • Written informed consent 		
Exclusion criteria <ul style="list-style-type: none"> • Inability to tolerate orally given morphine • History of widely fluctuating pain severity requiring parenteral administration of opiates • Scheduled to receive chemotherapy or radiation therapy within 1 month 		
Population <ul style="list-style-type: none"> • 29 male and female adults with chronic severe pain (underlying illnesses included cancer (76%), chronic severe back pain (6%), multiple sclerosis (6%), astrocytoma (6%), postherpetic neuralgia (6%)). 		
Interventions <ul style="list-style-type: none"> • SR morphine administered every 12 hours (7am and 7pm) Versus <ul style="list-style-type: none"> • IR morphine administered every 4 hours (starting at 7am) Supplemental IR morphine for breakthrough pain		
Outcomes <ul style="list-style-type: none"> • Pain intensity (measured at 7am, 11am, 3pm, 7pm, 11pm using a VAS (10cm long with the words “no pain” and excruciating pain” at each end), and the Present Pain Intensity (PPI) index of the McGill-Melzack Pain Questionnaire consisting of 6 adjectives (0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating) • Supplemental doses of morphine • Side effects (0 = none to 6 = intolerable) • Preference 		
Results Pain intensity – VAS (10cm long with the words “no pain” and excruciating pain” at each end)		
	SR	IR
Pain intensity - mean (SD)	1.36 (SD = 1.68)	1.57 (SD = 1.82)
The difference was not statistically significant (P = not reported)		
Supplemental morphine		
	SR	IR

Supplemental morphine – doses (total mg morphine)	84 (total 2330 mg morphine)	72 (total 2320 mg morphine)
The difference was not statistically significant (P = not reported)		
Side effects (0 = none to 6 = intolerable)		
The authors reported that only two side effects were serious enough to warrant statistical analysis.		
Side effect	SR	IR
Nausea - mean (SD)	0.44 (SD = 1.23)	0.58 (SD = 1.32)
Tiredness - mean (SD)	0.58 (SD = 1.21)	0.64 (SD = 1.30)
Neither difference was statistically significant (P = not reported)		
Preference		
Preferred the SR phase of treatment - 8/14 (57%)		
Preferred the IR phase of treatment - 6/14 (43%)		
General comments <ul style="list-style-type: none"> • Double blind • Method of allocation and concealment were unclear • Only 17/29 (59%) completed the study • Reasons for withdrawals were fully reported • ITT analyses were not performed 		

Citation: Christrup, L. L., Sjogren, P., Jensen, N. H., Banning, A. M., Elbaek, K., Ersboll, A. K. et al. (1999). Steady-state kinetics and dynamics of morphine in cancer patients: is sedation related to the absorption rate of morphine? <i>Journal of Pain & Symptom Management</i> , 18, 164-173.
Design: Randomised, double-blind/double dummy cross-over study Country: Denmark Aim: To compare the steady state pharmacokinetics of morphine and its metabolites, as well as pharmacodynamic responses (pain relief, sedation and reaction times), after administration of immediate-release (IR) and sustained-release (SR) tablets in cancer patients
Inclusion criteria <ul style="list-style-type: none"> • Outpatients • Severe cancer related pain • Stabilised on oral morphine • Informed consent
Exclusion criteria <ul style="list-style-type: none"> • Significant renal or hepatic impairment • Severe respiratory disease • Received radiation therapy or chemotherapy within 4 weeks • Disease expected to influence absorption, metabolism or elimination of morphine
Population <ul style="list-style-type: none"> • 18 male and female adult outpatients with cancer related pain
Interventions <ul style="list-style-type: none"> • SR morphine tablets every 12 hours Versus <ul style="list-style-type: none"> • IR morphine tablets every 6 hours
Outcomes <ul style="list-style-type: none"> • Pain intensity (100mm VAS ranging from 0mm = no pain to 100mm = worst pain imaginable) • Sedation (100mm VAS ranging from 0mm = completely awake to 100mm = impossible to stay awake) • Side effects (recorded if spontaneously reported) • Overall impression of the medication (very good, good, fair, bad, extremely bad) • Pharmacokinetics

<ul style="list-style-type: none"> Pharmacodynamics
<p>Results</p> <p><u>Pain intensity</u> There were no significant differences between the IR and SR formulation with respect to pain intensity (data not reported)</p> <p><u>Side effects</u> Reported side effects were constipation, nausea, myoclonus and fatigue. These were not reported by treatment. There were no significant differences between the IR and SR formulation with respect to side effects.</p> <p><u>Overall impression of the medications</u> There was no difference in terms of patients overall impressions of the two treatments</p>
<p>General comments</p> <ul style="list-style-type: none"> Double blind (using the double dummy technique) Methods of sequence generation and allocation concealment were unclear All patients entered a 7-day run-in period to confirm that their daily morphine dose requirements were stable before entry into the study Only data related to pharmacodynamics was reported Crossover to alternate tablet occurred on the morning of study day 5 During the study, patients were not allowed to take any other medication containing morphine. Ketobemidone and acetaminophen were used for breakthrough pain
<p>Citation: Cundiff, D., McCarthy, K., Savarese, J. J., Kaiko, R., Thomas, G., Grandy, R. et al. (1989). Evaluation of a cancer pain model for the testing of long-acting analgesics. The effect of MS Contin in a double-blind, randomized crossover design. <i>Cancer</i>, 63, 2355-2359.</p>
<p>Design: Randomised, double-blind/double dummy cross-over study</p> <p>Country: USA</p> <p>Aim: To compare oral sustained-release (SR) morphine sulphate tablets every 12 hours to IR morphine sulphate tablets every 4 hours in patients with cancer pain.</p>
<p>Inclusion criteria</p> <ul style="list-style-type: none"> Age \geq 18 years Required regular opioid analgesics Chronic cancer pain
<p>Population</p> <ul style="list-style-type: none"> 23 male and female adults with cancer related pain. Some used regular opioid analgesics at baseline (unclear exactly how many)
<p>Interventions</p> <ul style="list-style-type: none"> SR morphine tablets every 12 hour <p>Versus</p> <ul style="list-style-type: none"> IR morphine tablets every 4 hours <p>The first day's dose was calculated by means of a standard conversion table, to be approximately one third the morphine equivalent of the previous daily narcotic dose or at least 30mg morphine every 12 hours After achievement of acceptable analgesia and its maintenance for 48 hours in the first study arm, patients were switched to the alternate treatment regimen Supplemental IR morphine for breakthrough pain was provided on an "as needed" basis</p>
<p>Outcomes</p> <ul style="list-style-type: none"> Pain intensity (0 = none; 1 = light; 2 = moderate; 3 = severe) Pain frequency (0 = none; 1 = occasional; 2 = frequent; 3 = constant) Total morphine sulphate dose Rescue fraction Rescue dose Side effects
<p>Results</p>

Pain intensity (0 = none; 1 = light; 2 = moderate; 3 = severe)

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Mean pain intensity	2.21 ± 0.19	1.71 ± 0.16	0.79 ± 0.15	0.50 ± 0.17

The differences were not statistically significant (P = not reported)

Pain frequency (0 = none; 1 = occasional; 2 = frequent; 3 = constant)

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Mean pain frequency	2.14 ± 0.18	1.64 ± 0.17	1.00 ± 0.23	0.71 ± 0.27

The differences were not statistically significant (P = not reported)

Total morphine sulphate dose

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Total morphine sulphate dose (mg)	200 ± 51	275 ± 82	369 ± 113	496 ± 130

The difference was not statistically significant in the first 24 hours (P = not reported)

The difference in the last 24 hours was statistically significant (P ≤ 0.05)

Rescue fraction

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Rescue fraction (%)	39	28	11	5

The differences were not statistically significant (P = not reported)

Rescue dose

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Rescue dose (mg)	78 ± 24	77 ± 27	39 ± 14	23 ± 9

The differences were not statistically significant (P = not reported)

Side effects

Side effect	Duration (days)	No. patients	Medication phase
Dizziness	1	1	IR
Drowsiness	4	1	IR
Constipation	3.5	1	SR
Pruritus	1	1	IR

General comments

- Double blind
- Method of allocation and concealment were unclear
- Only 14/23 (61%) completed the study
- Reasons for withdrawals were fully reported
- ITT analyses were not performed

Citation: Dalton, R., Etzell, P., Loprinzi, C., Miser, A., Therneau, T., Dose, A. et al. (1989). Single-dose trial of sustained-release morphine sulphate for cancer pain relief [abstract]. *Proceedings of the American Society of Clinical Oncology*, 8, 336 (**Abstract**)

Design: RCT (parallel groups)

Country: USA

Aim: To compare the analgesic efficacy and toxicity of 30mg immediate-release (IR) morphine sulphate to 30 mg sustained-release (SR)-, 60 mg SR-, and 90 mg SR morphine.			
Inclusion criteria Not reported			
Exclusion criteria Not reported			
Population <ul style="list-style-type: none"> 68 patients with cancer related pain 			
Interventions This was a SINGLE DOSE RCT <ul style="list-style-type: none"> 30mg IR morphine sulphate 30 mg SR morphine sulphate 60 mg SR morphine sulphate 90mg SR morphine sulphate 			
Outcomes <ul style="list-style-type: none"> Pain relief (0-4 VAS anchored at opposite ends by “no relief” and “pain free” and a Likert scale) – rated hourly Side effects (0-4 VAS anchored at opposite ends by “none” and “severe” 			
Results			
Group	Hours to 50% relief		Side effects
	Likert Scale	Visual Analogue Scale	
30mg IR (n = 48)	3.8	3.6	2.8
30mg SR (n = 45)	3.6	3.4	2.3
60mg SR (n = 47)	4.4	3.8	3.5
90mg SR (n = 47)	6.1	5.3	4.7
<p>The data from the trial show that single doses of 90mg SR morphine gave slightly improved analgesia ($p < 0.001$) and increased toxicity ($p < 0.001$) when compared to 30mg IR morphine. The other doses of SR morphine did not significantly differ from IR morphine in toxicity or duration (all $p > 0.15$)</p>			
General comments <ul style="list-style-type: none"> Abstract only Single dose study Double blinded Method of randomisation and allocation concealment was unclear An initial un-blinded test dose of 30mg IR morphine enabled exclusion of patients with grossly inadequate pain relief or major toxicity 			

Citation: Deng YP, Xu GZ, Wang, K, et al. The steady-state concentration of morphine sulphate tablets and its clinical analgesic effect in cancer patients. Chinese Pharmaceutical Journal 32: 356-9. 1997.
Design: RCT (parallel groups; abstract) Country: China Aim: to compare immediate-release morphine sulphate (IRMS) with sustained release morphine (SRMS) cancer patients with moderate-severe pain.
Inclusion criteria Not reported

Exclusion criteria
Not reported
Population
N = 17
Interventions
SRMS: 30 mg sustained-release oral morphine 12 hourly for 7 days. IRMS: 10 mg immediate-release oral morphine 4 hourly for 7 days.
Outcomes
Results
“The effective analgesic rate (sum of rates of grade 2–4 pain relief) of both CRMS [= SRMS] and IRMS on the 5 th day medication was 100%” (p 356).
General comments
These data are only included in abstract form as the full article is published in Chinese. It is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.
References of Included Studies (For systematic reviews): NA

Citation: Deschamps, M., Band, P. R., Hislop, T. G., Rusthoven, J., Iscoe, N., Warr, D. et al. (1992). The evaluation of analgesic effects in cancer patients as exemplified by a double-blind, crossover study of immediate-release versus controlled-release morphine. <i>Journal of Pain & Symptom Management</i> , 7, 384-392.
Design: Randomised, double-blind/double-dummy, cross-over study Country: Canada Aim: To compare the effects of sustained-release (SR) and immediate-release (IR) morphine preparations in adult patients with moderate to severe cancer pain and report methodological approaches to pain evaluation
Inclusion criteria <ul style="list-style-type: none"> • Age ≥ 18 • Pain due to metastatic cancer of sufficient severity to warrant the use of opioids • Normal haematologic, hepatic and renal function • Mentally and physically competent to comply • Informed consent
Exclusion criteria <ul style="list-style-type: none"> • Undergoing active cancer treatment • Receiving pain control other than analgesic medications (e.g. radiation therapy, nerve block) • Inability to take oral medication • Inability to tolerate morphine • Requiring regular parenteral analgesics for pain control
Population <ul style="list-style-type: none"> • 20 adult patients with cancer related pain. All were using opiates (morphine/ oxycodone/ hydromorphone/ anileridine) before the study.
Interventions Titration phase established the daily morphine dose required for adequate pain control. <ul style="list-style-type: none"> • SR morphine every 12 hours at 8am and 8pm Or <ul style="list-style-type: none"> • IR morphine every 4 hours at 8am, 12pm, 4pm and 8pm Morphine doses were adjusted individually to obtain pain control with the least side effects
Outcomes Pain intensity (10cm VAS ranging from “no pain” to agonising pain”) Supplemental IR morphine Side effects (0 = none; 1 = mild; 2 = moderate; 3 = severe)

Results

Pain intensity (mean VAS cm ranging from “no pain” to agonising pain”) (SDs were not presented)

Day	SR morphine	IR morphine
1	1.3	1.2
2	1.1	1.2
3	1.2	1.5
4	1.4	1.5
5	1.3	1.2
6	1.4	1.3
7	1.2	1.8
1-7	1.3	1.4

There were no significant differences between the two groups in terms of pain intensity.

Supplemental IR morphine

SR morphine		IR morphine	
Number requiring supplementary morphine	Mean supplemental dose (SD)	Number requiring supplementary morphine	Mean supplemental dose (SD)
9	15.4mg (18.4mg)	10	23.7mg (23.8)

There was no statistically significant difference between IR and CR in terms of the requirement for supplemental morphine

Side effects (SDs were not presented)

(0 = none; 1 = mild; 2 = moderate; 3 = severe)

Side effect	SR morphine	IR morphine
Nausea	0.23	0.39
Vomiting	0.10	0.18
Constipation	0.67	0.35
Drowsiness	0.93	1.08
Dizziness	0.53	0.45
Restlessness	0.46	0.49
Agitation	0.54	0.63
Tiredness	0.85	1.12
Dryness of mouth	0.72	0.94

There were no significant differences between the two groups in terms of side effects.

General comments

- The study was double blinded (maintained by the double dummy technique)
- Randomisation was conducted by the pharmaceutical company using a randomisation table
- Eight patients failed to complete. ITT analyses not conducted.

Citation: Finn, J. W., Walsh, T. D., MacDonald, N., Bruera, E., Krebs, L. U., Shepard, K. V. et al. (1993). Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. *Journal of Clinical Oncology*, 11, 967-972.

Design: Randomised, double-blind/double-dummy, cross-over study

Country: USA

Aim: The study was performed with the following objectives: (1) to compare the analgesic efficacy of immediate-release morphine (IRM) administered every 4 hours and sustained-release morphine (SRM) administered every 12 hours orally to outpatients with severe pain due to cancer; (2) to evaluate the frequency and time occurrence of breakthrough pain; and (3) to assess the frequency of symptoms or side effects associated with oral morphine.

Inclusion criteria

- Age ≥ 18
- Pain due to advanced cancer
- Outpatients being cared for in their homes
- Pain that required treatment with a stable daily dose of at least 60mg of IRM
- Life expectancy of longer than 1 week, but less than 6 months

Population

37 adult patients with cancer related pain. Participants were receiving IRM every 4 hours at baseline.

Interventions

On day one of the study, all patients received their usual daily doses of IRM and baseline data were collected. On days 2 and 3 patients received:

- Active SRM 30mg every 12 hours and placebo oral solution every 4 hours

Or

- Active IRM 20mg/mL every 4 hours and placebo tablets identical to SRM every 12 hours

On day 4 patients were crossed over to alternate treatment, which they received for the subsequent 3 days (days 4-6).

The baseline dose range of morphine was 60-360mg/day and for SRM it was 60 – 300mg/day

Outcomes

- Analgesic efficacy (at 2pm and 9pm on days 1-6 using a 100 mm VAS. A difference of 25mm between VAS scores was specified pre-study as indicating clinically meaningful effect on days 3 and 6)
- Breakthrough pain
- Side effects (once a day, relating to the previous 24 hours)

Results

Analgesic efficacy (mean VAS rating on 100mm scale)

	Time			
	Noon	4pm	9pm	Overall
IRM baseline	21.71 ± 3.97	26.79 ± 5.07	25.04 ± 5.09	24.51 ± 2.72
IRM	20.00 ± 4.07	19.40 ± 4.15	20.08 ± 4.33	20.00 ± 2.42
SRM	18.80 ± 3.67	18.20 ± 4.07	22.50 ± 4.30	19.80 ± 2.32

There were no statistically significant differences at any measurement time point.

Breakthrough pain

	Number of patients experiencing breakthrough pain				
	No breakthrough pain during treatment with SRM or IRM	Breakthrough pain during both SRM and IRM	Breakthrough pain during IRM but not SRM	Breakthrough pain during SRM but not IRM	P
No. patients (N = 34)	29	2	0	3	0.25

Side effects (mean VAS scores)

Variable	Time		
	Noon	4pm	9pm
IRM	9.8 ± 3.38	10.9 ± 3.76	15.8 ± 5.04
SRM	10.3 ± 2.94	9.5 ± 2.93	9.3 ± 3.01
Sedation			
IRM	34.4 ± 6.15	30.1 ± 5.63	40.0 ± 6.41
SRM	26.3 ± 5.61	29.6 ± 5.48	40.03 ± 6.23
Anxiety			
IRM	28.3 ± 5.98	26.9 ± 5.90	27.5 ± 5.76
SRM	27.5 ± 5.01	23.8 ± 4.89	25.9 ± 5.28
Depression			
IRM	22.9 ± 5.17	20.8 ± 5.01	25.2 ± 5.36
SRM	29.1 ± 4.85	21.3 ± 4.41	22.8 ± 4.71

There were no statistically significant differences between groups in terms of side effects

General comments

- Randomisation and allocation concealment were sufficient
- The study was double blinded (maintained by the double dummy technique)
- 25/34 (74%) patients who completed the study were female
- Mean age was 59
- ITT analyses were not performed
- Three patients did not complete the six day study (two chose to withdraw; one died on day 5)
- Demographic characteristics were equivalent in each group at baseline

Citation: Gillette, J. F. (1997). Double-blind crossover clinical and pharmacokinetic comparison of oral morphine syrup and sustained release morphine sulfate capsules in patients with cancer-related pain. <i>Clinical Drug Investigation</i> , 14, 22-27.																																															
Design: Randomised, double-blind/double-dummy, cross-over study Country: France Aim: To evaluate the efficacy and bioavailability of a new sustained-release (SR) morphine sulphate formulation																																															
Inclusion criteria <ul style="list-style-type: none"> • Age \geq 18 years • Normal renal and hepatic function • End stage cancer 																																															
Exclusion criteria <ul style="list-style-type: none"> • Oncological treatment within 4 weeks of study entry • Severe nausea or vomiting • Contraindications to opiate drugs 																																															
Population 35 male and female adults with advanced cancer and severe pain. Pain was not controllable by step 2 analgesics (according to WHO criteria)																																															
Interventions <ul style="list-style-type: none"> • SR morphine capsules every 12 hours (8am and 8pm) Versus <ul style="list-style-type: none"> • Immediate-release (IR) morphine syrup every 4 hours (4am, 8am, 12pm, 4pm, 8pm, 12am) 6 day treatment regimen A stabilisation period was conducted to achieve satisfactory pain relief with IR morphine (up to 300mg/day)																																															
Outcomes <ul style="list-style-type: none"> • Pain intensity (assessed 4 times daily at 10am, 2pm, 6pm, 10pm) on a 100mm VAS) • Adverse events • Side effects • Pharmacokinetics 																																															
Results <u>Pain intensity</u> (assessed 4 times daily at 10am, 2pm, 6pm, 10pm) on a 100mm VAS) Mean \pm SD <table border="1"> <thead> <tr> <th></th><th>SR morphine</th><th>IR morphine</th></tr> </thead> <tbody> <tr> <td>Baseline</td><td>83.0 \pm 14.3mm</td><td>82.4 \pm 11.4mm</td></tr> <tr> <td>Mean over study period</td><td>10.1 \pm 2.1mm</td><td>10.5 \pm 2.4mm</td></tr> </tbody> </table> <p>There were no significant differences between groups in terms of pain scores.</p> <u>Adverse events</u> (no. patients (%)) <table border="1"> <thead> <tr> <th></th><th>SR morphine</th><th>IR morphine</th></tr> </thead> <tbody> <tr> <td>Patients with \geq 1 AE</td><td>25 (93%)</td><td>25 (93%)</td></tr> <tr> <td>Withdrawal because of AE</td><td>0 (0%)</td><td>0 (0%)</td></tr> </tbody> </table> <p>There were no significant differences between groups in terms of adverse events.</p> <u>Side effects</u> (no. patients (%)) <table border="1"> <thead> <tr> <th></th><th>SR morphine</th><th>IR morphine</th></tr> </thead> <tbody> <tr> <td>Constipation</td><td>14 (52%)</td><td>16 (60%)</td></tr> <tr> <td>Nausea</td><td>11 (41%)</td><td>11 (41%)</td></tr> <tr> <td>Dry mouth</td><td>21 (78%)</td><td>20 (74%)</td></tr> <tr> <td>Somnolence</td><td>15 (55%)</td><td>14 (52%)</td></tr> <tr> <td>Dizziness</td><td>1 (4%)</td><td>2 (7%)</td></tr> <tr> <td>Agitation</td><td>6 (22%)</td><td>3 (11%)</td></tr> <tr> <td>Euphoria</td><td>4 (15%)</td><td>2 (7%)</td></tr> <tr> <td>Pruritus</td><td>4 (15%)</td><td>5 (19%)</td></tr> </tbody> </table>				SR morphine	IR morphine	Baseline	83.0 \pm 14.3mm	82.4 \pm 11.4mm	Mean over study period	10.1 \pm 2.1mm	10.5 \pm 2.4mm		SR morphine	IR morphine	Patients with \geq 1 AE	25 (93%)	25 (93%)	Withdrawal because of AE	0 (0%)	0 (0%)		SR morphine	IR morphine	Constipation	14 (52%)	16 (60%)	Nausea	11 (41%)	11 (41%)	Dry mouth	21 (78%)	20 (74%)	Somnolence	15 (55%)	14 (52%)	Dizziness	1 (4%)	2 (7%)	Agitation	6 (22%)	3 (11%)	Euphoria	4 (15%)	2 (7%)	Pruritus	4 (15%)	5 (19%)
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Nightmares	3 (11%)	4 (15%)
Urinary retention	1 (4%)	1 (4%)

There were no significant differences between groups in terms of side effects.

General comments

- Method of randomisation and allocation concealment was unclear
- Double blind
- Placebo used

Citation: Hanks, G. W., Twycross, R. G., Bliss, J. M., Hanks, G. W., Twycross, R. G., & Bliss, J. M. (1987). Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. *Anaesthesia*, 42, 840-844.

Design: Randomised, double-blind/double-dummy, cross-over study

Country: UK

Aim: To compare 4 hourly aqueous morphine sulphate and twice daily sustained-release morphine tablets.

Inclusion criteria

- Patients with advanced cancer admitted to hospital based continuing care
- Pain that was controlled by 4 hour aqueous morphine sulphate in aqueous solution
- Received the same dose of morphine for at least 7 days

Exclusion criteria

- Patients who were too or confused
- Pain not stable

Population

- 27 patients male and female adults with cancer related pain. All participants had their pain controlled by 4 hour aqueous morphine sulphate in aqueous solution at baseline

Interventions

- SR morphine tablets twice a day (10am and 10pm)
Versus
- Immediate-release (IR) aqueous morphine (6am, 10am, 2pm, 6pm, 10pm, and for some patients 2am)

Outcomes

- Pain intensity (0 – 100 VAS scale)
- Side effects (0 – 100 VAS)

Results

Pain intensity

	SR morphine	IR morphine
Initial	80.2 (5.0)	86.1 (2.8)
Final	75.3 (7.2)	82.4 (4.8)
Median change (95% CI)	0.0 (-55.0 - 70.0)	0.0 (-51.0 - 60.0)
P	0.948	

Side effects

	Alertness		Nausea		Mood		Sleep		Appetite	
	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR
Initial	78.8 (4.1)	51.7 (8.0)	86.9 (3.1)	84.8 (3.6)	15.2 (4.2)	14.9 (4.6)	28.6 (6.7)	16.3 (4.3)	24.9 (7.2)	19.1 (6.5)
Final	75.2 (6.0)	81.7 (4.3)	85.8 (5.1)	87.8 (3.7)	14.5 (4.8)	18.5 (5.4)	13.6 (3.1)	22.3 (4.5)	32.0 (8.0) 32.0 (8.0)	28.8 (8.4)
Median change (95% CI)	-0.5 (-8.1 - 15.3)	-20.5 (-46.3 - -13.6)	0.5 (-9.2 - 11.5)	-2.5 (-11.5 - 5.5)	1.0 (-4.1 - 5.6)	-0.5 (-10.2 - 3.1)	6.5 (3.3- 26.8)	-2.0 (-15.8 - 3.7)	0.0 (-17.7 - 3.4)	1.0 (24.1 ± 4.7)
P	0.007		0.339		0.266		0.017		0.938	

That is, IR morphine seemed to be associated with improved alertness while SR morphine seemed to be associated with improved quality of sleep, but it should be noted that the groups differed at baseline on these measures.

General comments

- Method of allocation and concealment were unclear
- Only 18/27 (67%) completed the study. Reasons for withdrawals were fully reported. No ITT analysis.
- Double blinded

Citation: Kaplan, R., Parris, W. C., Citron, M. L., Zhukovsky, D., Reder, R. F., Buckley, B. J. et al. (1998). Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *Journal of Clinical Oncology*, 16, 3230-3237.

Design: RCT (parallel groups)

Country: USA

Aim: To compare the efficacy, acceptability of therapy, and safety of sustained-release (SR) oxycodone tablets with immediate-release (IR) oxycodone tablets in patients with cancer related pain.

Inclusion criteria

- Being treated with a strong single entity opioid or 10 or more tablets per day of a fixed dose opioid/non-opioid analgesic
- Receiving a stable opioid dose
- Stable coexistent disease
- Written informed consent

*After the study had begun, these criteria eliminated by an amendment to facilitate enrolment into the study

Population

- 164 male and female adults with cancer pain (108 before protocol amendment; 72 after protocol amendment)

Interventions

- IR oxycodone

Versus

- SR oxycodone

The original protocol did not allow dose titration or use of supplemental analgesics for breakthrough pain. Patients whose pain was not effectively controlled at the initial oxycodone dose calculated from previous opioid use were discontinued from the study. The protocol was subsequently amended to include open label titration with IR oxycodone before participants were randomised to double blind treatment, and the use of IR oxycodone 5mg tablets as supplemental analgesic. Supplemental doses could be taken no more frequently than every 4 hours.

Outcomes

- Dose administered
- Pain intensity
- Acceptability of therapy
- Discontinuation
- Side effects

Results

Dose administered (mean)

SR oxycodone (n=78)	IR oxycodone (n = 82)
127mg (range 40-640mg)	114mg (range 20 – 400mg)

Pain intensity (average of daily assessments for all 5 days)

SR oxycodone (n=78)	IR oxycodone (n = 82)
1.3±0.1	1.3±0.1

*NB values were identical

Acceptability of therapy

	SR oxycodone (n=78)	IR oxycodone (n = 82)
Baseline	3.5±0.1	3.5±0.1
End of study	3.2±0.1	3.2±0.1

*NB values were identical

Discontinuation

Reported separately for those who entered study before versus after amendment of the protocol

	Titration and rescue allowed (n = 55)				No titration or rescue (n = 105)			
	SR (n = 28)		IR (n = 27)		SR (n = 50)		IR (n = 55)	
	No.	%	No.	%	No.	%	No.	%
Lack of acceptable pain control	1	4	5	19	17	34	17	31
Adverse event	2	7	3	11	4	8	7	13
Other reason	3	11	2	7	6	12	5	9
All reasons	6	21	10	37	27	54	29	53

Side effects

Side effects	SR oxycodone (n=78)			IR oxycodone (n = 82)		
	Patients		No. of reports	Patients		No. of reports
	No.	%		No.	%	
Nausea	14	18	16	21	26	30
Somnolence	14	18	16	17	21	18
Constipation	9	12	9	17	21	17
Vomiting	8	10	11	14	17	23
Dizziness	5	6	6	11	13	14
Sweating	4	5	5	3	4	3
Asthenia	3	4	4	8	10	9
Nervousness	3	4	3	5	6	5
Dry mouth	3	4	3	5	6	5
Pruritus	2	3	3	4	5	4
Insomnia	2	3	2	4	5	4
Headache	0	0	0	6	7	7
Anxiety	0	0	0	4	5	4

Overall significantly fewer adverse events were reported for CR oxycodone compared with IR oxycodone ($p = 0.006$)

There were significantly fewer adverse events associated with the digestive system in the SR oxycodone group than the IR oxycodone group ($p = \text{not reported}$)

Fewer patients in the SR oxycodone group reported headache compared with the IR oxycodone group ($p = 0.029$).

General comments

- Double blind
- Unclear methods of sequence generation and allocation concealment
- Exclusion criteria were eliminated mid way through the study by an amendment to facilitate enrolment into the study
- The study protocol was altered mid way through the study to include open label titration with IR oxycodone before participants were randomised to double blind treatment, and the use of IR oxycodone 5mg tablets as supplemental analgesic.
- 96% of patients took $\geq 90\%$ of doses of study medication

Citation: Klepstad, P., Kaasa, S., Jystad, A., Hval, B., Borchgrevink, P. C., Klepstad, P. et al. (2003). Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain*, 101, 193-198.

Design: RCT (parallel groups)

Country: Norway

Aim: To compare the efficacy of oral immediate-release (IR) morphine titration and sustained-release (SR) morphine

titration in a randomised double blind controlled study				
Inclusion criteria <ul style="list-style-type: none">• Age ≥ 18 years• Pain despite ongoing treatment for weak to mild pain• Chronic cancer pain				
Exclusion criteria <ul style="list-style-type: none">• Weak opioids not titrated to maximal recommended dose• Morphine intolerance• Decreased gastrointestinal uptake of oral medications• Scheduled transfer from hospital				
Population <ul style="list-style-type: none">• 40 male and female adults with cancer related pain despite treatment with opioids for mild to moderate pain				
Interventions <ul style="list-style-type: none">• SR morphine tablets once daily Versus <ul style="list-style-type: none">• IR morphine tablets every 4 hours				
Outcomes <ul style="list-style-type: none">• Time to acceptable pain relief• Pain intensity (daily average for the previous 24 hours on a 100mm VAS anchored at one end by “no pain” and at the opposite end by “unbearable pain”)• Side effects (VRS where 1 = not at all; 2 = some; 3 = severe; 4 = very severe)• Health related quality of life (at end of study using QLQ-C30)				
Results <u>Days to acceptable pain relief</u> Mean (95% CI)				
SR morphine (n = 19)		IR morphine (n = 15)		
1.7 (1.7 – 2.0)		2.1 (1.4 – 2.7)		
There was no statistically significant difference between groups in terms of time to acceptable pain relief.				
<u>Pain intensity (daily average for the previous 24 hours on a 100mm VAS)</u> Mean (95% CI)				
SR morphine (n = 19)		IR morphine (n = 15)		
22 (14 – 29)		26 (17 – 36)		
There was no statistically significant difference between groups in terms of pain intensity.				
<u>Side effects</u> (intensity of symptoms before and after titration on a VRS where 1 = not at all; 2 = some; 3 = severe; 4 = very severe) Mean (95% CI)				
	Baseline		After titration	
	SR	IR	SR	IR
Nausea	1.9 (1.4-2.4)	1.6 (1.2-1.9)	1.6 (1.3-1.9)	1.6 (1.3-2.0)
Tiredness	2.5 (2.2-2.9)	2.6 (2.2-3.0)	1.9 (1.5-2.2)	2.4 (2.0-2.8)
Constipation	2.1 (1.5-2.6)	1.7 (1.2-2.2)	1.9 (1.4-2.4)	1.7 (1.2-2.2)
Appetite	2.6 (2.0-3.1)	2.4 (1.8-3.0)	2.3 (1.8-2.7)	2.4 (1.9-2.9)
Vertigo	1.3 (1.0-1.5)	1.4 (1.0-1.8)	1.4 (1.1-1.7)	1.5 (1.1-1.8)
Lack of sleep	2.2 (1.6-2.8)	2.0 (1.4-2.6)	1.6 (1.1-2.0)	1.3 (1.0-1.5)
Patients titrated with IR morphine reported significantly more tiredness at the end of titration. There were no other significant differences between the two groups in terms of side effects.				
<u>Health related quality of life (before and after titration; scores range from 1-100, higher scores indicate better functioning)</u> Mean (95% CI)				
	Before titration		After titration	
	IR	SR	IR	SR
Physical function	35 (22-48)	48 (34-63)	35 (22-49)	46 (29-62)

Role function	17 (5-28)	33 (19-47)	15 (0.3-30)	30 (13-46)
Emotional function	78 (69-87)	70 (61-79)	73 (62-85)	67 (57-77)
Cognitive function	70 (58-81)	59 (45-74)	68 (53-82)	74 (62-87)
Social function	49 (33-65)	43 (27-60)	46 (25-66)	44 (28-61)
Quality of life	44 (34-55)	37 (25-50)	42 (34-50)	44 (35-53)

There were no statistically significant differences between groups in terms of health related quality of life.

General comments

- Double blind (using the double dummy technique)
- Methods of randomisation unclear.
- Allocation concealment adequate

Citation: Knudsen J, Mortensen SM, Eikard B, & Henriksen H. Slow-release morphine tablets compared with conventional morphine tablets in the treatment of cancer pain. *Ugeskrift for Læger* 147; 780-4. 1985.

Design: Randomised, double-blind/double-dummy, cross-over study

Country:

Aim: To compare immediate-release morphine tablets (IRM) to sustained-release morphine tablets (SRM) in patients with moderate-severe cancer pain.

Inclusion criteria

Patients with ≥ 7 days of well-functioning treatment with IRM in constant 4-hourly dosing for moderate-severe pain from metastatic/invasive cancer which was not rapidly progressing. The patients also had to be judged physically and psychologically able to maintain a fixed dosage schedule and to complete questionnaires at fixed time points throughout a 2-week period.

Exclusion criteria

Intercurrent disease or occurrence of moribund condition

Population

N = 18 (2 of whom dropped out), 10 females, age range 39-66 years

Interventions

2 weeks duration (1 week of each treatment) - Same 24-hour dose was given of each treatment

IRM: 4-hourly tablets

SRM: 12-hourly tablets

Outcomes

Pain, sedation, side effects, patient preference

Results

Pain at individual time points (pain measured 2-hourly 7 times per day) and in total: IRM = SRM

Pain at each of the 7 days, and days 1-3 and 5-7 combined : IRM = SRM

Sedation at individual time points or days and days 5-7 combined: IRM = SRM

Sedation at days 1-3 combined: IRM < SRM ($p < 0.02$)

Side-effects: Nausea: N = 5 and 6 for SRM and IRM, respectively. Vomiting: N = 2 and 3 for SRM and IRM, respectively.

Dizziness: N = 3 and 2 for SRM and IRM, respectively.

Patient preference: N = 3 indicated that they preferred SRM, N = 8 preferred IRM and N = 5 preferred both equally.

General comments

Published in Danish

Not first-line treatment

Unclear allocation concealment

References of Included Studies (For systematic reviews): NA

Citation: Levy, M. H., Fitzmartin, R., & Reder, R. (1993). Comparison of immediate versus controlled release morphine (MS Contin) in the long-term management of cancer-related pain [abstract]. *Proceedings of the American Society of Clinical Oncology*, 12, 455 (**Abstract**)

Design: RCT (parallel groups)

Country: UK

Aim: To compare the use of immediate-release (IR) morphine tablets to sustained-release (SR) morphine tablets in the

long term management of pain in patients with advanced cancer
Inclusion criteria <ul style="list-style-type: none"> • Cancer related pain
Population <ul style="list-style-type: none"> • 65 adults with cancer related pain
Interventions <ul style="list-style-type: none"> • SR morphine tablets Versus <ul style="list-style-type: none"> • IR morphine tablets (no further details reported)
Outcomes <ul style="list-style-type: none"> • Pain intensity • Side effects • Adverse events
Results <u>Pain</u> Pain intensity was mild in both groups (data not reported) <u>Side effects</u> Side effects were similar in both groups (data not reported) <u>Adverse events</u> Three reported: severe confusion (SR and IR); severe hypotension (SR).
General comments <ul style="list-style-type: none"> • Abstract only • Open label • Method of randomisation and allocation concealment unclear • Number of days in the study ranged from 1-608. 44/65 (68%) completed at least 4 weeks, and the primary analysis was based on this period

Citation: MacDonald, N., Bruera, E., Michaud, M., Brennels, C., Tennant, A., Walsh, T. D. et al. (1987). A double-blind, cross-over comparison between slow-release morphine (SRM) and short acting morphine (SAM) in the treatment of cancer pain. <i>Proceedings of the Annual Meeting of the American Society of Clinical Oncology</i> (Abstract)
Design: Randomised, double-blind, cross-over study (Abstract) Country: Canada Aim: To determine whether a sustained-release (SR) morphine preparation could adequately replace a less convenient formulation
Inclusion criteria <ul style="list-style-type: none"> • Advanced cancer • Receiving narcotics for the treatment of stable cancer pain
Exclusion criteria Not reported
Population <ul style="list-style-type: none"> • 28 patients with cancer related pain
Interventions <ul style="list-style-type: none"> • SR morphine every 12 hours Versus <ul style="list-style-type: none"> • Immediate-release (IR) morphine every 4 hours in an equivalent daily dose
Outcomes <ul style="list-style-type: none"> • Pain intensity • Supplementary morphine • Side effects
Results

	Baseline (mean)	SR morphine (mean)	IR morphine (mean)
Pain intensity at noon	20 ± 25	26 ± 21	18 ± 16
Pain intensity at 4pm	26 ± 22	22 ± 20	17 ± 16
Pain intensity at 9pm	25 ± 18	25 ± 20	19 ± 15
Number of supplemental doses of morphine	.30 ± .56	.58 ± .91	.33 ± .51
Sleeplessness	35 ± 25	32 ± 23	32 ± 20
Nausea	12 ± 15	8 ± 9	8 ± 8
Depression	14 ± 19	11 ± 15	10 ± 11
Anxiety	20 ± 20	15 ± 15	12 ± 11

There were no statistically significant differences between the two groups

General comments

- Abstract only
- Unclear whether the study was blinded
- Method of randomisation and allocation concealment was unclear

Citation: Panich, A., & Charnvej, L. (1993). Comparison of morphine slow release tablet (MST) and morphine sulphate solution (MSS) in the treatment of cancer pain. *Journal of the Medical Association of Thailand*, 76, 672-676.

Design: Randomised, single-blind (assessor) crossover study without placebo-control

Country: Thailand

Aim: To compare the effect of oral morphine, morphine sulphate sustained-release (SR) tablets and morphine sulphate solution for the treatment of pain in cancer patients

Inclusion criteria

- Cancer patients referred to a pain clinic

Exclusion criteria

- Unconscious
- Unable to speak

Population

23 male and female adults with severe cancer related pain

Interventions

- SR morphine tablets (30mg) every 12 hour
- Versus
- Immediate-release (IR) morphine solution every (5-10mg) 4 hours

Cross-over design. Each phase was 7 days long.

Supplemental morphine available

At the end of the study patients were prescribed their preferred medication

Outcomes

- Pain intensity (measured at 8am and 4pm everyday using a 10cm VAS, a pain rating scale administered by a nurse (0 = no pain; 1 = mild; 2 = moderate; 3 = severe))
- Sleep duration
- Side effects
- Patient preference

Results

Pain intensity (mean ± SD)

	Before	Day 4	Day 5	Day 6	Day 7
SR					
VAS	5.9 ± 1.3	3.5 ± 2.0	3.3 ± 1.9	3.3 ± 2.1	3.2 ± 2.0
Nurse rating	2.4 ± 0.5	1.4 ± 0.9	1.4 ± 0.8	1.4 ± 0.7	1.3 ± 0.8
IR					
VAS	5.9 ± 1.3	3.1 ± 1.8	3.0 ± 1.7	2.9 ± 1.9	2.8 ± 1.9
Nurse rating	2.4 ± 0.5	1.4 ± 0.7	1.4 ± 0.7	1.2 ± 0.7	1.2 ± 0.7

There were no significant differences between groups in terms of pain scores.

Sleep duration

	Before	Day 4	Day 5	Day 6	Day 7
SR					
Daytime	3.3 ± 1.1	4.2 ± 1.5	4.1 ± 1.3	4.1 ± 1.3	4.2 ± 1.3
Night time	5.6 ± 1.7	6.9 ± 1.4	7.2 ± 1.3	7.2 ± 1.3	7.3 ± 1.1
IR					
Daytime	3.3 ± 1.1	4.3 ± 1.2	4.3 ± 1.3	4.4 ± 1.3	4.3 ± 1.3
Night time	5.6 ± 1.7	7.1 ± 1.7	7.3 ± 1.3	7.4 ± 1.4	7.5 ± 1.1

There were no significant differences between groups in terms of sleep duration.

Side effects

Side effect	SR Cases (%)	IR Cases (%)
Nausea & vomit	16 (32.6 %)	17 (34.7 %)
Constipation	21 (42.8 %)	16 (32.6 %)
Stupor	3 (6.1 %)	6 (12.2 %)
Dizziness	19 (38.8 %)	11 (22.45 %)
Anorexia	0 (0 %)	0 (0 %)
Itching	1 (2.0 %)	1 (2.0 %)
Tight in chest	2 (4.8 %)	0 (0 %)

There were no significant differences between groups in terms of side effects.

Patient preference

Chose SR: 14/49 (29%)

Chose IR: 35/49 (71%)

The difference between groups was significant ($p = 0.0002$). It is worth noting that 66% of patients were ENT patients who had difficulty swallowing tablets.

General comments

- Method of randomisation and allocation concealment was unclear
- Not placebo-controlled
- Single blind (assessor)
- 24/73 (33%) withdrew from the study. Reasons for drop-outs was fully reported.

Citation: Parris, W. C., Johnson, B. W., Jr., Croghan, M. K., Moore, M. R., Khojasteh, A., Reder, R. F. et al., (1998). The use of controlled-release oxycodone for the treatment of chronic cancer pain: a randomized, double-blind study. *Journal of Pain & Symptom Management*, 16, 205-211.

Design: RCT (parallel groups)

Country: France

Aim: To compare the effectiveness and safety of sustained-release (SR) oxycodone tablets with immediate-release (IR) oxycodone tablets in patients with chronic cancer pain

Inclusion criteria

- Age ≥ 18 years
- Cancer patients receiving 6 to 12 tablets or capsules a day of fixed-combination analgesics (opioid/non-opioid) for cancer-related pain
- Stable coexistent disease
- Written informed consent

Exclusion criteria

- Pain not already acceptably controlled
- Surgery or radiotherapy in prior 10 days
- Anticipated radiotherapy or surgery during study period
- Compromised functioning of a major organ system
- Receiving non-opioid analgesics (concomitant non-analgesic therapies were allowed during study)

Population

- 111 male and female adults with cancer pain

Interventions

- 30mg of SR oxycodone tablets every 12 hours daily for 5 days
- Versus
- 15mg of IR oxycodone four times daily for 5 days

Outcomes

- Pain intensity (rated in a daily diary in the morning (overnight pain), midday (morning pain rating), evening (afternoon pain), and bedtime (evening pain) on a four point categorical (CAT) scale (0 = none; 1 = slight; 2 = moderate; 3 = severe)
- Acceptability (rated on a 5 point CAT scale: 1 = very poor; 2 = poor; 3 = fair; 4 = good; 5 = excellent)
- Discontinuation rates
- Adverse events (assessors contacted patients daily by telephone and recorded information about adverse events and changes in condition daily)

Results

Pain intensity (average of the 4 CAT scale ratings on each study day)

	SR (mean \pm SE)	IR (mean \pm SE)
Mean baseline pain scores	1.5 \pm 0.1	1.3 \pm 0.1
Overall mean pain intensity scores (treatment completers)	1.4 \pm 0.1	1.1 \pm 0.1

A graph presents the mean daily scores. It was not of sufficient quality to enable accurate extraction of the data. There were no statistically significant differences between the CR and IR groups in terms of pain intensity ($P > 0.05$).

Acceptability

There were said to be no significant differences between treatment groups. Data was not reported. A graph presents the results, but it is not possible to extract accurate data. Mean acceptability scores by day were fair to good throughout the study period.

Discontinuation rates

37% of patients discontinued the 5-day study. There was no significant difference between treatment groups. Data was not reported.

Adverse events

Number of patients reporting at least one adverse event (considered by the investigators to be at least possibly related to treatment)

	SR	IR
At least one adverse event	36/52 (69%)	36/51 (70%)

Leaving the study due to adverse event(s)

	SR	IR
Leaving study due to adverse event(s) (%)	4/52 (8%)	7/51 (14%)

No patients died during the study

	Cancer patients	
Side effect, n (%)	SR n = 51	IR n = 52
Nausea	11 (20)	13 (24)
Somnolence	13 (24)	12 (22)
Dizziness	8 (15)	10 (19)
Constipation	12 (22)	10 (19)
Vomiting	5 (9)	11 (20)
Pruritus	7 (13)	5 (9)

Headache	7 (13)	3 (6)
Dry mouth	4 (7)	3 (6)
Sweating	1 (2)	5 (9)
Abdominal pain	3 (6)	1 (2)
Insomnia	3 (6)	1 (2)

There were no statistically significant differences between the two groups in terms of the incidence of adverse events, although there was a trend toward less nausea, vomiting and sweating in patients receiving SR oxycodone.

General comments

- This was a double blind study
- 94% of patients treated were at least 95% compliant
- Many of the outcomes are reported in insufficient detail to allow data extraction

<p>Citation: Poulain, P., Krakowski, I., Lakdja, F., Maynadier, J., Petot, P., Salamagne, M., Hauseux, P., Saudubray, F., Bonny, N., and Lechevne, J. [French multicentre therapeutic trial of slow-release morphine sulfate (Moscontin) in the treatment of neoplastic pain]. SO: Therapie 45[4], 364. 1990.</p>
<p>Design: Open-label, randomised, cross-over study (Abstract)</p> <p>Country: France</p> <p>Aim: to compare immediate-release morphine (IRMS) to sustained-release morphine (SRMS) for the treatment of pain in cancer patients.</p>
<p>Inclusion criteria</p> <p>Not reported</p>
<p>Exclusion criteria</p> <p>Not reported</p>
<p>Population</p> <p>N = 84</p>
<p>Interventions</p> <p>IRMS: 2 successive treatment every 4 hours</p> <p>SRMS: 2 successive treatments every 12 hours</p>
<p>Outcomes</p> <p>Patient preference, pain control, side effects.</p>
<p>Results</p> <p>N = 6 excluded due to worsening condition, treatment intolerance, and radiotherapy.</p> <p>N = 78 in the analysis.</p> <p>Patient preference: N = 10 preferred IRMS, N = 59 preferred SRMS, N = 8 did not indicate preference.</p> <p>Side effects: IRMS = SRMS. > 50% of all patients experienced drowsiness and constipation.</p> <p>Morphine dose necessary to achieve stable state of analgesia: Mean SRMS is 10 mg lower per day than IRMS.</p>
<p>General comments</p> <p>- Open label</p> <p>- These data are only published in abstract form and it is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.</p>
<p>References of Included Studies (For systematic reviews): NA</p>

<p>Citation: Ranchere, J. Y., Vedrenne, J., Esteve, M., Roquefeuil, B., Kong, A., Siou, D. et al. (1991). Slow release morphine suspension versus morphine sulfate tablet (MST): a multicentre study in cancer pain. <i>European Journal of Cancer</i>, 27, S286. (Abstract)</p>
<p>Design: Multicenter, randomised, double-blind/double-dummy, cross-over study</p> <p>Country: France</p> <p>Aim: To compare sustained-release (SR) morphine suspension with morphine sulphate tablets</p>

Inclusion criteria <ul style="list-style-type: none"> • Cancer related pain
Population <ul style="list-style-type: none"> • 52 cancer patients
Interventions <ul style="list-style-type: none"> • SR morphine tablets Versus <ul style="list-style-type: none"> • Immediate-release (IR) morphine suspension (no further details reported)
Outcomes <ul style="list-style-type: none"> • Pain (self reported) • Quality of life (self reported) • Adverse events (assessor rated) • Patient preference
Results <u>Pain (self reported)</u> There was no significant difference between groups (data not reported) <u>Quality of life (self reported)</u> There was no significant difference between groups (data not reported) <u>Adverse events (assessor rated)</u> There was no significant difference between groups (data not reported) <u>Patient preference</u> There was no significant difference between groups (data not reported)
General comments <ul style="list-style-type: none"> • Abstract only • Double blind • Method of randomisation and allocation concealment was unclear

Citation: Salzman, R. T., Roberts, M. S., Wild, J., Fabian, C., Reder, R. F., Goldenheim, P. D. et al., (1999). Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? <i>Journal of Pain & Symptom Management</i> , 18, 271-279.
Design: RCT (parallel groups) Country: USA Aim: To determine whether patients with chronic pain could be titrated to stable pain control as readily with sustained-release (SR) as with an immediate-release (IR) formulation of oral oxycodone
Inclusion criteria <ul style="list-style-type: none"> • Age ≥ 18 years • Stable chronic pain not adequately controlled by prior analgesic therapy with or without opioids • Written informed consent
Exclusion criteria <ul style="list-style-type: none"> • Allergy or contraindication to opioid therapy • History of substance abuse • Patients receiving an opioid analgesic that could not be discontinued • Cancer patients prescribed oral oxycodone at a total dose of more than 400mg/day • Non-cancer patients prescribed oral oxycodone at a total rate of more than 80mg/day
Population <ul style="list-style-type: none"> • <u>Study 1:</u> 48 male and female adults with cancer pain • <u>Study 2:</u> 57 male and female adults with moderate to severe lower back pain despite analgesic therapy
Interventions Two separate trials comparing: <ul style="list-style-type: none"> • SR oral oxycodone (administered every 12 hours (8am and 8pm \pm 1 hour)) Versus

- IR oral oxycodone (administered every 4 hours (8am, 2pm, 8pm and bedtime \pm 1 hour)

For opioid naive patients, the starting dose was 20mg/day. The starting dose was titrated upward in each study to a limit of 400mg/day for cancer patients and to 80mg/day for non-cancer patients or until patients rated their level of pain intensity at no greater than "slight". Dose adjusted every 24 to 48 hours as necessary.

Supplemental analgesic was permitted as needed for control of breakthrough or incident pain

Outcomes

- Stable analgesia
- Time to stable analgesia
- Final mean daily dose
- Pain intensity
- Patient rated pain intensity on a four point categorical scale (0 = none; 1 = slight; 2 = moderate; 3 = severe) recorded in a daily diary and assessed at the clinic visit at end of titration period
- Time to stable pain control (rated as zero in patients meeting criteria for success in the first 48 hours). Among cancer patients, titration rated successful if pain stabilised within a maximum of 21 days; among non-cancer patients, the time limit was 10 days.
- Adverse events recorded in a daily diary and assessed at the clinic visit at end of titration period

Results Only results for the cancer patients are reported.

Proportion achieving stable analgesia

Cancer patients	
SR n = 24	IR n = 24
22 (92%)	19 (79%)

Time to stable pain control

Cancer patients	
SR n = 24	IR n = 24
1.6 \pm 0.4	1.7 \pm 0.6

There was no significant difference between groups in terms of time to stable pain control.

Pain intensity

(Mean decrease from baseline \pm SE)

Cancer patients	
SR n = 24	IR n = 24
0.7 \pm 0.2 (P = 0.01)	0.3 \pm 0.2 (P = 0.14)

Final mean daily doses

Cancer patients	
SR n = 24	IR n = 24
104mg (SE = 20)	113mg (SE = 24)

Patient assessment of pain intensity at baseline and end of titration (0 = none; 1 = slight; 2 = moderate; 3 = severe)

	Cancer patients	
	SR n = 19	IR n = 16
Baseline	1.8 (0.2)	1.4 (0.2)
End of titration	1.1 (0.2)	1.1 (0.1)

Side effects (only those occurring in greater than 10% of patients in at least one of the 4 treatment groups)

Side effect, n (%)	Cancer patients	
	SR n = 24	IR n = 24
Somnolence	9 (37)	7 (29)
Nausea	7 (29)	5 (21)
Vomiting	5 (21)	3 (12)

Postural hypotension	5 (21)	4 (17)
Constipation	4 (17)	9 (37)
Pruritus	4 (17)	0 (0)
Confusion	3 (12)	2 (8)
Dry mouth	3 (12)	1 (4)
Dizziness	2 (8)	0 (0)
Nervousness	2 (8)	4 (17)
Asthenia	2 (8)	1 (4)
Headache	1 (4)	1 (4)

General comments

- Two studies were reported. Patients with cancer participated in one study; patients who had chronic, moderate to severe back pain (despite analgesic therapy) participated in the other
- Participants in both studies were predominantly white and female
- 91% of patients reported taking an opiate-containing medication(s) prior to study entry
- Most patients were converted to the study drug from a variety of fixed-combination or single entity opioid therapies
- This was an open-label study
- There were no significant differences between groups on demographic variables at baseline in either study
- Withdrawals were fully reported with reasons

Citation: Stambaugh, J. E., Reder, R. F., Stambaugh, M. D., Stambaugh, H., Davis, M., Stambaugh, J. E. et al., (2001). Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. *Journal of Clinical Pharmacology*, 41, 500-506.

Design: Randomised, double-blind, cross-over study

Country: USA

Aim: To evaluate the efficacy of oral sustained-release (SR) oxycodone, given as twice daily dosing, as compared with immediate-release (IR) oxycodone given twice a day in patients with cancer pain. The study was designed to (1) to determine if the clinical efficacy and achievable plasma concentrations of oxycodone in the SR form as seen in prior studies were comparable to the IR form (2) to confirm the doses of SR every 12 hours provided equivalent analgesia to doses of IR oxycodone given 4 times a day.

Inclusion criteria

- Age \geq 18 years
- Moderate or severe cancer related pain
- Ability to take oral medication
- Informed consent

Exclusion criteria

- Requirement for greater than 240mg/day oral oxycodone equivalent for pain relief
- Primary tumor or metastatic disease in the brain
- Received chemotherapy within 3 days of study entry
- Substance misuse
- Severe cognitive impairment
- Compromised renal or hepatic function
- Received radiotherapy to the site of pain
- Hypersensitivity to oxycodone

Population

- 40 male and female adults with moderate or severe cancer related pain

Interventions

Consisted of three periods with a duration of less than 35 days: a titration period of 2 – 21 days followed by two crossover periods

- (1) Initial open-label titration period to stabilise patients on IR oxycodone (4 times daily).
- (2) Participants randomised to double blind treatment:

- Immediate release oxycodone

Versus

- Controlled release oxycodone
- (3) Crossover at the same daily dose

Outcomes

- Global pain (over the past 24 hours) and current pain on a scale of 0-10 (0 = no pain; 10 = severe pain)
- Current pain relief (0 = no relief; 10 = complete relief)
- Global acceptability (over the past 24 hours) and current acceptability on a scale of 1-5 (1 = very poor; 2 = poor; 3 = fair; 4 = good; 5 = excellent)
- Side effects

Results

Global (over previous 24 hours) pain intensity (during double blind periods)

	End of double blind periods			
Global pain intensity	Start of titration	IR oxycodone	SR oxycodone	P value
Mean (SD)	6.0 (2.2)	2.8 (1.9)	2.7 (1.9)	0.8804

Current pain relief and plasma concentrations of oxycodone (during double blind periods)

	IR oxycodone		SR oxycodone		p-value
Time	Mean	SD	Mean	SD	
Current pain relief					
0.75-1.5 hours	6.8	3.3	6.9	3.6	0.8318
2-4 hours	7.6	3.0	8.1	2.8	0.3018
Plasma concentrations					
0 hours	32.9	29.7	38.7	36.0	0.1966
0.75-1.5 hours	50.4	39.0	38.0	41.0	0.1184
2-4 hours	51.0	40.8	41.9	51.0	0.3571

Side effects (during double blind periods)

	IR oxycodone (n = 31)			SR oxycodone (n = 30)		
	Number	%	Reports	Number	%	Reports
Nausea	4	13	4	3	10	3
Dizziness	3	10	3	3	10	3
Somnolence	3	10	5	2	7	4
Asthenia	2	6	2	2	7	2
Pruritus	1	3	1	2	7	2
Sweating	2	6	2	1	3	1
Constipation	1	3	1	1	3	1
Dry mouth	1	3	1	1	3	1
Nervousness	0	0	0	1	3	1
Vomiting	2	6	2	0	0	0
Total	10	32	21	10	33	21

General comments

- Method of sequence generation and allocation concealment unclear
- Double blind
- Opioids other than the study medication were prohibited
- 25% (10/40) discontinued the study. Reasons for drop-outs were fully reported
- Pain intensity scores and blood samples were obtained with 100% compliance from the 30 completers

Citation: Thirlwell, M. P., Sloan, P. A., Maroun, J. A., Boos, G. J., Besner, J. G., Stewart, J. H. et al. (1989). Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. <i>Cancer</i> , 63, 2275-2283.																			
Design: Randomised, double-blind/double-dummy, cross-over study Country: Canada Aim: To compare the pharmacokinetics and clinical efficacy of immediate-release (IR) morphine sulphate solution and sustained-release (SR) morphine sulphate tablets																			
Inclusion criteria <ul style="list-style-type: none">• Age ≥ 18 years• Requiring oral opioid therapy for cancer related pain• Mentally and physically competent to comply with therapeutic protocol• Written informed consent																			
Exclusion criteria <ul style="list-style-type: none">• Hepatic or renal impairment• Severe nausea and/or vomiting• Uncontrolled pain requiring frequent parenteral morphine• Scheduled to receive a course of chemotherapy or radiotherapy in the 7 days before or anytime during the trial																			
Population <ul style="list-style-type: none">• 23 male and female adults with cancer related pain. Some used regular opioid analgesics at baseline (unclear exactly how many)																			
Interventions <ul style="list-style-type: none">• SR morphine tablets every 12 hour Versus <ul style="list-style-type: none">• IR morphine tablets every 4 hours Cross-over design. Each phase was at least 5 days long. Supplemental IR morphine for breakthrough pain Opioid dose before the study dictated starting trial dose																			
Outcomes <ul style="list-style-type: none">• Pain intensity (0 = none; 1 = mild; 2 = moderate; 3 = severe)• Side effects• Supplemental morphine• Pharmacokinetics																			
Results <u>Pain intensity (mean)</u> <table><tr><td>SR morphine (n = 18)</td><td>IR morphine (n = 18)</td><td>P</td></tr><tr><td>0.55 ± 0.58</td><td>0.57± 0.63</td><td>0.85</td></tr></table> <u>Side effects (frequency)</u> <table><tr><td></td><td>SR morphine (n = 18)</td><td>IR morphine (n = 18)</td></tr><tr><td>Nausea</td><td>3</td><td>3</td></tr><tr><td>Dizziness</td><td>3</td><td>3</td></tr></table> There were no statistically significant differences between groups in terms of the frequency or severity side effects <u>Supplemental morphine (no. patients requiring extra dose)</u> <table><tr><td>SR morphine (n = unclear)</td><td>IR morphine (n = unclear)</td></tr><tr><td>3</td><td>3</td></tr></table>	SR morphine (n = 18)	IR morphine (n = 18)	P	0.55 ± 0.58	0.57± 0.63	0.85		SR morphine (n = 18)	IR morphine (n = 18)	Nausea	3	3	Dizziness	3	3	SR morphine (n = unclear)	IR morphine (n = unclear)	3	3
SR morphine (n = 18)	IR morphine (n = 18)	P																	
0.55 ± 0.58	0.57± 0.63	0.85																	
	SR morphine (n = 18)	IR morphine (n = 18)																	
Nausea	3	3																	
Dizziness	3	3																	
SR morphine (n = unclear)	IR morphine (n = unclear)																		
3	3																		
General comments <ul style="list-style-type: none">• Double blind (using the double dummy technique)• Method of allocation and concealment were unclear• Reasons for withdrawals were fully reported• ITT analyses were not performed																			

Citation: Ventafridda, V., Saita, L., Barletta, L., Sbanotto, A., De, C. F., Ventafridda, V. et al. (1989). Clinical

observations on controlled-release morphine in cancer pain. <i>Journal of Pain & Symptom Management</i> , 4, 124-129.
Design: RCT (parallel groups) Country: Italy Aim: To conduct a clinical comparison between sustained-release (SR) morphine sulphate tablets and immediate-release (IR) morphine solution.
Inclusion criteria <ul style="list-style-type: none"> Advanced cancer patients
Exclusion criteria <ul style="list-style-type: none"> No strong narcotics in past month
Population <ul style="list-style-type: none"> 70 male and female adults with cancer related pain. Patients had not taken strong narcotics in the past month.
Interventions <ul style="list-style-type: none"> SR morphine tablets Versus <ul style="list-style-type: none"> IR morphine solution Depending on the analgesic response to previous treatments, initial doses of CR morphine varied from 20mg/day to a maximum of 120mg/day. Initial doses of IR morphine varied from a minimum of 24mg/day to a maximum of 144mg/day as 4% solution
Outcomes <ul style="list-style-type: none"> Pain intensity Drug dosage and dosing intervals Side effects
Results <u>Pain intensity</u> Mean daily pain scores were reported on a graph. Data could not be extracted. The mean difference in pain score from day 1 to 14 was 19.4 in the IR group and 22.5 in the SR group. There was no significant difference between groups (p = not reported). <u>Drug dosage and dosing intervals</u> Mean daily dosages were reported on a graph. Data could not be extracted. There was a non significant difference between mean dosages administered from day 1 – 14 (p = .20) <u>Side effects</u> Mean daily side effect scores were reported on a graph. Data could not be extracted. The frequency of daily side effects was lower in patients on SR morphine than IR. These differences were significant for itching (p = .001), dry mouth (p = .001), drowsiness (p = .001), nausea (p = .001), vomiting (p = .001), headache (p = 0.01), constipation (p = .001). There were non-significant differences in terms of trembling and restlessness.
General comments <ul style="list-style-type: none"> An additional study of SR morphine was carried out concurrently. This was not an RCT The study was not blinded Method of allocation and concealment were unclear Only 32/70 (46%) completed the study Reasons for withdrawals were fully reported ITT analyses were not performed Results were not well reported
Citation: Walsh, T. D. (1985). Controlled study of oral slow-release morphine in pain due to advanced cancer. <i>Proceedings of the Annual Meeting of the American Society of Clinical Oncology</i> (Abstract).
Design: Randomised, double-blind/double-dummy, cross-over study Country: UK Aim: To compare the clinical analgesic efficacy and side effects of a new sustained-release morphine tablet given 12 hourly to immediate-release (IR) morphine.
Inclusion criteria

<ul style="list-style-type: none"> • Cancer related pain
Population <ul style="list-style-type: none"> • 36 male and female adults with cancer related pain
Interventions <ul style="list-style-type: none"> • SR morphine tablets 12 hourly <p>Versus</p> <ul style="list-style-type: none"> • IR morphine liquid formulation 4 hourly
Outcomes <ul style="list-style-type: none"> • Pain • Side effects
Results <u>Pain</u> Analysis by paired/unpaired t-tests and contingency tables revealed no significant differences in analgesic efficacy between the two preparations <u>Side effects</u> Analysis by paired/unpaired t-tests and contingency tables revealed no significant differences in side effects between the two preparations
General comments <ul style="list-style-type: none"> • Abstract only • Double blind • Method of randomisation and allocation concealment was unclear

Citation: Walsh, T. D., MacDonald, N., Bruera, E., Shepard, K. V., Michaud, M., Zanes, R. et al. (1992). A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. <i>American Journal of Clinical Oncology</i> , 15, 268-272.
Design: Randomised, double-blind/double-dummy, cross-over study Country: UK Aim: To compare the safety and efficacy of sustained-release (SR) and immediate-release (IR) morphine in patients with advanced cancer
Inclusion criteria <ul style="list-style-type: none"> • Cancer related pain
Exclusion criteria <ul style="list-style-type: none"> • Two or more parenteral doses of morphine for breakthrough pain during the 24 hours of the baseline day • Unstable fluctuating pain • Unable to take regular oral medication
Population <ul style="list-style-type: none"> • 33 male and female adults with cancer related pain. Patients were taking morphine at study entry.
Interventions <ul style="list-style-type: none"> • SR morphine tablets 12 hourly <p>Versus</p> <ul style="list-style-type: none"> • IR morphine liquid formulation 4 hourly
Outcomes <ul style="list-style-type: none"> • Pain (100mm VAS) • Side effects

Results

Pain (100mm VAS)

Mean (SD)

	12pm	4pm	9pm	Overall
SR	27.78 (5.13)	20.63 (4.30)	26.06 (4.30)	24.82 (2.64)
IR	22.00 (4.75)	16.04 (3.25)	21.02 (3.44)	19.69 (2.23)

There were no statistically significant differences between groups in terms of pain scores.

Side effects

Mean (SD)

		12pm	4pm	9pm
Nausea	IR	9.0 (2.26)	12.9 (4.01)	5.8 (1.65)
	SR	10.4 (3.25)	9.3 (3.21)	9.9 (3.82)
Sedation	IR	33.6 (5.51)	38.5 (5.87)	37.3 (5.57)
	SR	35.6 (5.85)	33.4 (5.16)	39.1 (6.59)
Anxiety	IR	19.0 (4.05)	11.2 (2.93)	12.9 (3.15)
	SR	11.0 (3.10)	15.1 (4.24)	16.8 (5.03)
Depression	IR	12.2 (3.77)	8.4 (2.15)	9.3 (3.60)
	SR	12.4 (3.60)	13.0 (3.96)	11.0 (3.38)

There were no statistically significant differences between groups in terms of side effects.

General comments

- Double blind
- Double dummy technique used
- Method of randomisation and allocation concealment adequate

Citation: Xu, G. Z., Cai, Z. J., Li, T. D., Liu, A. G., Xie, G. R., Liu, S. M., Chen, C. H., Ma, Q. L., Hou, J., Deng, Y. P., and Lu, X. X. [Clinical evaluation of analgesic effect of controlled release morphine sulphate tablets in patients with cancer pain]. SO: The Chinese Journal of Clinical Pharmacology 11[2], 88-97. 1995.

Design: RCT ((parallel groups; abstract)

Country: China

Aim: to compare immediate-release morphine sulphate (IRMS) with sustained-release morphine (SRMS) cancer patients with moderate-severe pain.

Inclusion criteria

Not reported

Exclusion criteria

Not reported

Population

N = 262

Interventions

SRMS: 30 mg sustained-release oral morphine 12 hourly (N = 101) for 6 days.

SRMS: 60 mg sustained-release oral morphine 12 hourly (N = 58) for 6 days.

IRMS: 10 mg immediate-release oral morphine 4 hourly (N = 103) for 6 days.

Outcomes

Pain intensity difference, sum of pain intensity difference, pain relief, total pain relief, rate of pain relief over grade 2 and total analgesic score.

Results

“Clinical results showed that there was no significant difference between the two treatment groups” (p 97).

General comments

- Double-blind

- These data are only included in abstract form as the full article is published in Chinese. It is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

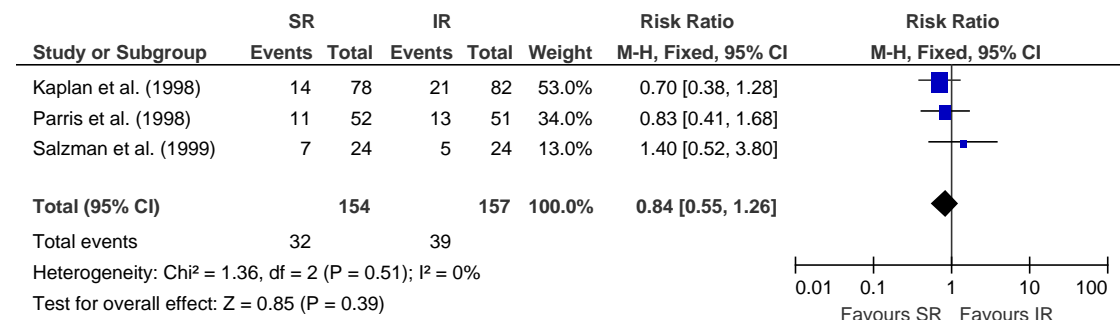
References of Included Studies (For systematic reviews): NA

Summary table of the results of the meta-analyses of IR v SR oxycodone of topic 2a

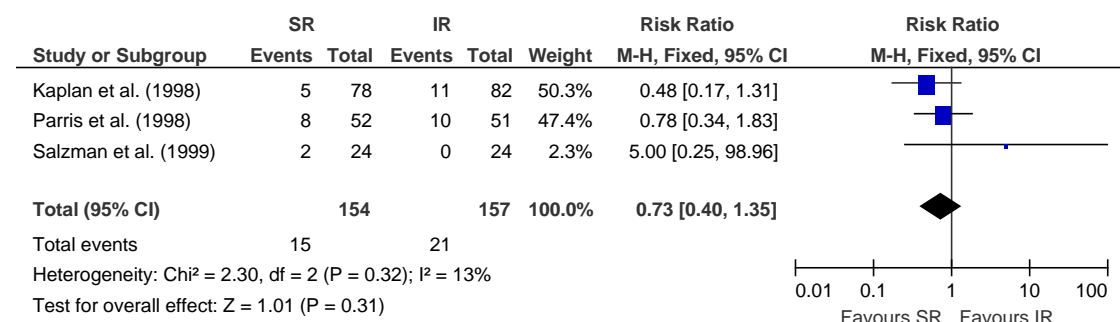
Side effect	Studies	Participants	Statistical method	Effect size (Risk Ratio) [95% CI]
Nausea	3	311	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.26]
Dizziness	3	311	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.40, 1.35]
Drowsiness	3	311	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.68, 1.52]
Vomiting	3	311	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.45, 1.44]
Constipation	3	311	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.44, 1.12]
Pruritus	3	311	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.64, 3.18]
Dry mouth	3	311	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.47, 2.71]
Nervousness	2	208	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.20, 1.63]
Asthenia	2	208	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.18, 1.47]
Headache	3	311	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.16, 1.63]
Sweating	2	263	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.09, 4.19]

Forest plots of the results of review question 2a

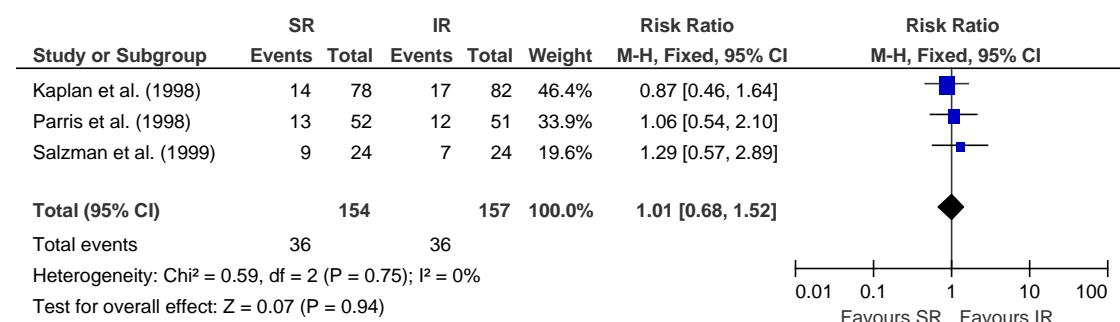
Nausea



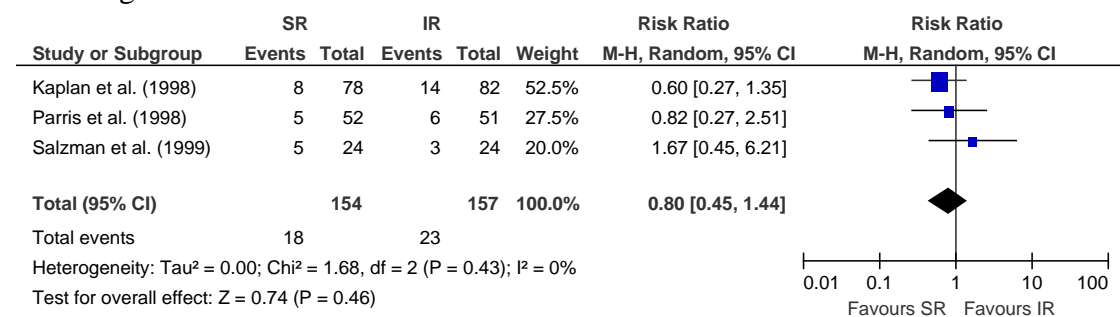
Dizziness



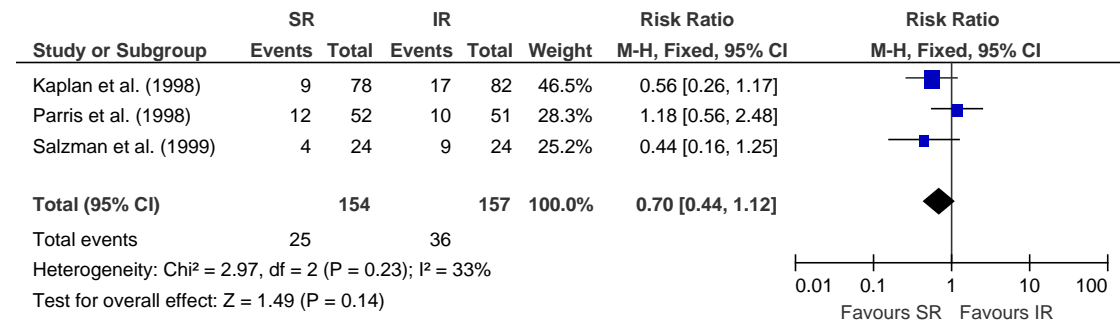
Drowsiness



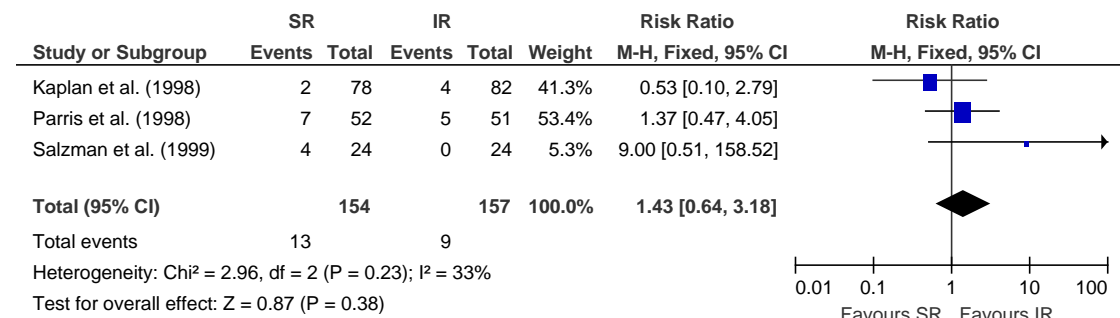
Vomiting



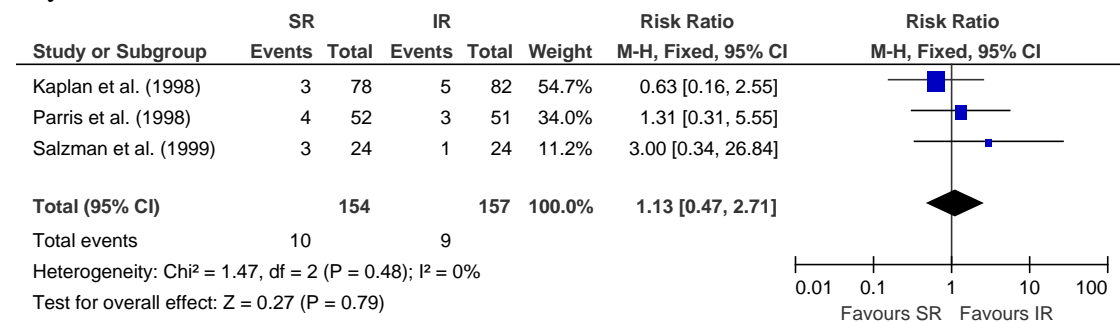
Constipation



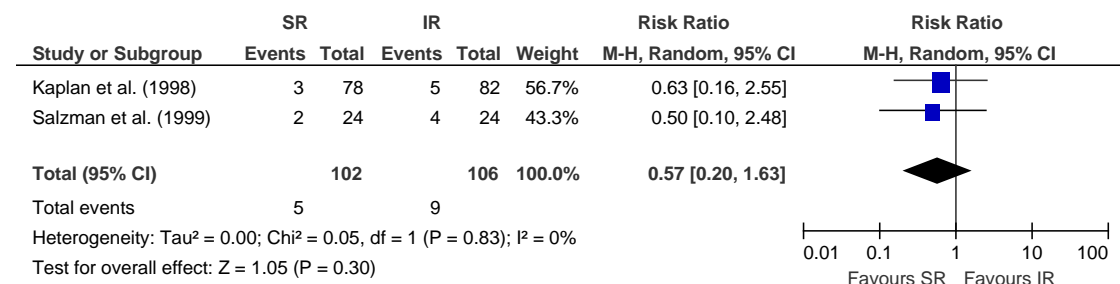
Pruritus



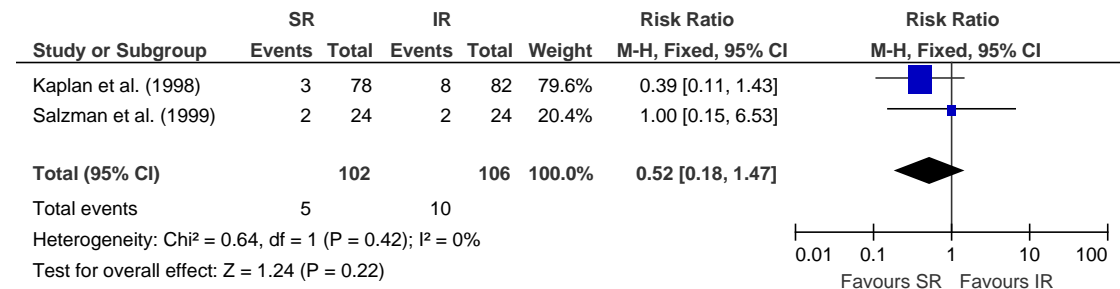
Dry mouth



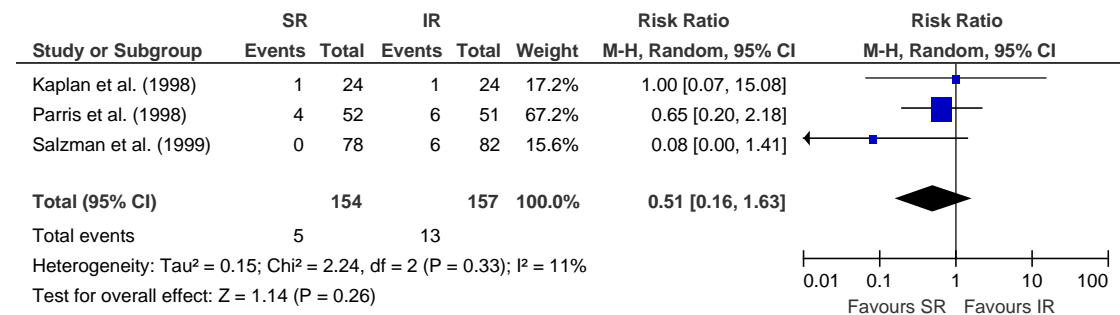
Nervousness



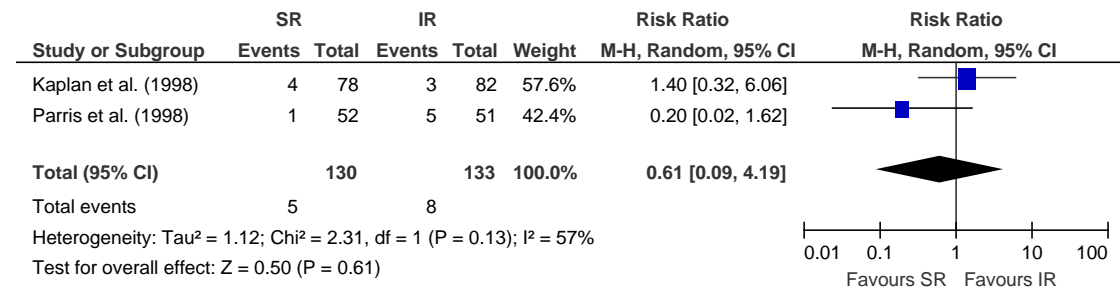
Asthenia



Headache



Sweating



3.4 First-line maintenance treatment

2b: Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl/buprenorphine) as first-line maintenance treatment for pain in patients with advanced and progressive disease who require strong opioids?

Evidence table 3

<p>Citation: Bekkering, G. E., Soares-Weiser, K., Reid, K., Kessels, A. G., Dahan, A., Treede, R. D., and Kleijnen, J. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. <i>Current Medical Research and Opinion</i> 27[7], 1477-1491. 2011.</p>
<p>Design: Systematic review of RCTs with network meta-analysis Country: International Aim: To evaluate the evidence available to support the position of morphine as the reference standard for step III opioids on efficacy and tolerability outcomes.</p>
<p>Inclusion criteria RCTs that evaluated the efficacy or tolerability of step III opioids in patients aged > 18 years and suffering from cancer-related or non-cancer-related chronic pain. Studies had to compare an oral or transdermal step III opioid to placebo or to another step III opioid and report on ≥ 1 of the pre-specified outcomes of efficacy (pain intensity (PI), pain relief (PR), Patient Global Impression of Change (PGIC), quality of sleep (QoS), quality of life (QoL)) or tolerability (treatment discontinuations (TD), severe adverse events (SAE)) after ≥ 24 hours of treatment.</p>
<p>Exclusion criteria Studies with a cross-over design, with N = 1, on breakthrough pain, on acute flare-ups of chronic pain, on intravenous opioids and on tapentadol.</p>
<p>Population <u>Morphine v transdermal fentanyl:</u> 5 RCTs - Allan et al. (2005): Low back pain; age range 21-90 years, 61% females; Fentanyl (57 µg/h) N = 338, morphine (140 mg/day) N = 342, study duration of 12-24 months; outcomes were PR, QoL, TD, SAE - Mercadante et al. (2008): Cancer pain; age range 18-78 years, 48.6% females; Fentanyl (1.18 mg/day) N = 36, morphine (82.7 mg/day) N = 36, study duration of 7 days-1 month; outcomes were PI, QoL, TD - Öztürk et al. (2008) [did not provide data that could be used in the meta-analysis]: Cancer pain; mean age 55 years, NR females; Fentanyl (25-100 µg/h) N = 25, morphine (20, 60, 120, 200 µg/day) N = 25, study duration of 7 days-1 month; outcome was PI - Van Seventer et al. (2003) [patients with mild-moderate pain]: Cancer pain; age range 21-91 years, 35.1% females; Fentanyl (67 µg/h) N = 67, morphine (105 mg/day) N = 64, study duration of 7 days-1 month; outcomes were PI, PR, PGIC, QoS, TD, SAE - Wong et al. (1997): Cancer pain; age range 30-79 years, 27.5% females; Fentanyl (61.3 µg/h) N = 20, morphine (174 mg/day) N = 20, study duration of 7 days-1 month; outcomes were PI, QoS, QoL <u>Morphine v oxycodone:</u> 4 RCTs - Mucci-LoRusso et al. (1998): Cancer pain; age range 30-83 years, 45% females; Oxycodone (101 mg/day) N = 48, morphine (140 mg/day) N = 52, study duration of 7 days-1 month; outcomes were PI, PGIC, TD - Mercadante et al. (2010): Cancer pain; mean age range 63.2 years, 59% females; Oxycodone (20 mg/day, increased as needed) N = 30, morphine (30 mg/day, increased as needed) N = 30, study duration of 1-2 months; outcomes were PI, TD - Nicholson et al. (2006) [patients with moderate-severe non-malignant pain]: Non-cancer pain; age range 20-83 years, 50.5% females; Oxycodone (34-84.7mg/day) N = 54, morphine (30-78.7 mg/day) N = 43, study duration of 6-11 months; outcomes were PI, PGIC, QoS, QoL, TD, SAE - Rauck et al. (2006): Moderate-severe chronic low back pain; age range 28-73 years, 61% females; Oxycodone (53.3 mg/day) N = 189, morphine (63.7 mg/day) N = 203, study duration of 1-2 months; outcomes were PI, PR, QoL, TD, SAE <u>Morphine v transdermal buprenorphine:</u> 1 RCT - Pace et al. (2007): Cancer pain; mean age 54.5 years, 48.1% females; Buprenorphine (35-52.5 µg/h) N = 26, morphine (60-90 mg/day) N = 26, study duration of 1-2 months; outcomes were PI, PGIC, QoL, QoS.</p>
<p>Interventions Sustained-release morphine v sustained-release oxycodone Sustained-release morphine v transdermal fentanyl Sustained-release morphine v transdermal buprenorphine</p>

Outcomes

Pain intensity, treatment discontinuation

Results

Significant between-study heterogeneity precluded pair-wise meta-analyses. The results reported below are a result of network meta-analyses.

Effectiveness (pain intensity):

Sustained-release morphine v sustained-release oxycodone:

- Treatment duration 1 day – 1 week: Weighted mean difference (WMD) = 3.3 (95% CI -1.2 – 7.8), non-significant.
- Treatment duration 1 week – 1 month: WMD = 3.4 (95% CI -0.4 – 7.2), non-significant.
- Treatment duration > 1 month: WMD = 3.9 (95% CI -1.4 – 9.2), non-significant.
- Studies on cancer pain: WMD = 2.3 (95% CI -5.4 – 10.1), non-significant.
- Studies on non-cancer pain: **WMD = 4.6 (95% CI 0.1 – 9.1), significant. That is, in patients with non-cancer pain sustained-release morphine was significantly more effective than sustained-release oxycodone.**

Sustained-release morphine v transdermal fentanyl:

- Treatment duration 1 day – 1 week: WMD = 5.8 (95% CI -0.7 – 12.4), non-significant.
- Treatment duration 1 week – 1 month: **WMD = 8.8 (95% CI 4.2 – 13.4), significant.**
- Treatment duration > 1 month: WMD = 1 (95% CI -32.6 – 34.6), non-significant.
- Studies on cancer pain: **WMD = 8.7 (95% CI 2.7 – 14.7), significant. That is, in patients with cancer pain sustained-release morphine was significantly more effective than transdermal fentanyl.**
- Studies on non-cancer pain: WMD = 6.7 (95% CI -0.1 – 13.6), non-significant

Sustained-release morphine v transdermal buprenorphine:

- Treatment duration 1 day – 1 week: -
- Treatment duration 1 week – 1 month: **WMD = 9.6 (95% CI 3.6 – 15.6), significant. That is, in patients with treatment duration of 1 week to 1 month sustained-release morphine was significantly more effective than transdermal buprenorphine.**
- Treatment duration > 1 month: **WMD = -16.4 (95% CI -30.3 – 2.5), significant. That is, in patients with treatment duration of > 1 month transdermal buprenorphine was significantly more effective than sustained-release morphine.**
- Studies on cancer pain: **WMD = -16.4 (95% CI -29 – 3.8), significant. That is, in patients with cancer pain transdermal buprenorphine was significantly more effective than sustained-release morphine.**
- Studies on non-cancer pain: -

Treatment discontinuation (due to any reason): Studies on cancer pain

- Sustained-release morphine v sustained-release oxycodone: Odds ratio (OR) = 0.86 (95% CI 0.32 – 2.3), non-significant.
- Sustained-release morphine v transdermal fentanyl: **OR = 0.43 (95% CI 0.24 – 0.75), significant. That is, the odds of treatment discontinuation due to any reason were reduced in patients receiving transdermal fentanyl compared to patients receiving sustained-release morphine.**
- Sustained-release morphine v transdermal buprenorphine: **OR = 0.11 (95% CI 0.03 – 0.46), significant. That is, the odds of treatment discontinuation due to any reason were reduced in patients receiving transdermal buprenorphine compared to patients receiving sustained-release morphine.**

Treatment discontinuation (due to lack of efficacy): Studies on cancer pain

- Sustained-release morphine v sustained-release oxycodone: OR = 1.09 (95% CI 0.07 – 17.8), non-significant.
- Sustained-release morphine v transdermal fentanyl: OR = 1.2 (95% CI 0.39 – 3.65), non-significant.
- Sustained-release morphine v transdermal buprenorphine: OR = 0.48 (95% CI 0.07 – 3.14), non-significant.

Treatment discontinuation (due to adverse events): Studies on cancer pain

- Sustained-release morphine v sustained-release oxycodone: OR = 0.51 (95% CI 0.12 – 2.17), non-significant.
- Sustained-release morphine v transdermal fentanyl: **OR = 0.12 (95% CI 0.04 – 0.36), significant. That is, the odds of treatment discontinuation due to adverse events were reduced in patients receiving transdermal fentanyl compared to patients receiving sustained-release morphine.**
- Sustained-release morphine v transdermal buprenorphine: -

Öztürk et al. (2008):

- Pain intensity: Transdermal fentanyl = sustained-release morphine.
- **Constipation: Transdermal fentanyl (27%/N = 6) < sustained-release morphine (64%/N = 14), p = 0.03.**
- Nausea/vomiting, urinary retention, and urticaria: Transdermal fentanyl = sustained-release morphine.
- No patients developed hypoventilation

General comments

Comprehensive search of 10 databases (conducted in December 2010)
Explicit search strategy

Data extraction performed by 1 reviewer and checked by 2nd reviewer
Each study quality appraised using the Cochrane Collaboration checklist by 2 reviewers independently
Independent screening of database by 2 reviewers
Some studies not on population of interest

References of Included Studies (For systematic reviews):

- Allan, L., Richarz, U., Simpson, K., et al. Transdermal fentanyl versus sustained-release oral morphine in strong-opioid naive patients with chronic low back pain. *Spine* 30, 2484-90. 2005.
- Mercadante, S., Porzio, G., Ferrera, P., Fulfaro, F., Alelli, F., Verna, L., Villari, P., Ficarella, C., Gebbia, V., Riina, S., Casuccio, A., and Mangione, S. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. *European Journal of Pain* 12[8], 1040-1046. 2008.
- Mercadante, S., Tirelli, W., David, F., Arcara, C., Fulfaro, F., Casuccio, A., Gebbia, V., Mercadante, Sebastiano, Tirelli, Walter, David, Fabrizio, Arcara, Carlo, Fulfaro, Fabio, Casuccio, Alessandra, and Gebbia, Vittorio. Morphine versus oxycodone in pancreatic cancer pain: a randomized controlled study. *Clinical Journal of Pain* 26[9], 794-797. 2010.
- Mucci-LoRusso, P., Berman, B. S., Silberstein, P. T., Citron, M. L., Bressler, L., Weinstein, S. M., Kaiko, R. F., Buckley, B. J., Reder, R. F., Mucci-LoRusso, P., Berman, B. S., Silberstein, P. T., Citron, M. L., Bressler, L., Weinstein, S. M., Kaiko, R. F., Buckley, B. J., and Reder, R. F. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *European Journal of Pain: Ejp* 2[3], 239-249. 1998.
- Nicholson, B., Ross, E., Sasaki, J., Weil, A., Nicholson, Bruce, Ross, Edgar, Sasaki, John, and Weil, Arnold. Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled-release oxycodone HCl in moderate to severe non-malignant pain. *Current Medical Research & Opinion* 22[8], 1503-1514. 2006.
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- Rauck, R.L., Bookbinder, S.A., Bunker, T.R., et al. The ACTION study: A randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulphate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. *J Opioid Manag* 3, 155-6. 2006.
- van, Seventer R., Smit, J. M., Schipper, R. M., Wicks, M. A., and Zuurmond, W. W. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. *SO: Current medical research and opinion* 19[6], 457-469. 2003.
- Wong J.O., Chiu, G.L., Tsao, C.J., et al. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anaesthesiol Sinica* 35, 25-32. 1997.

Citation: Caraceni, A., Pigni, A., Brunelli, C., Caraceni, Augusto, Pigni, Alessandra, and Brunelli, Cinzia. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. *Palliative Medicine* 25[5], 402-409. 2011.

Design: Systematic review w/o/ meta-analysis

Country: Italy

Aim: To evaluate the evidence that oral morphine can be recommended as the first choice opioid in the treatment of moderate to severe cancer pain.

Inclusion criteria

RCTs, or meta-analyses of reported data, conducted in human, adult patients with chronic cancer pain reporting data on patient reported efficacy and/or side effects of morphine administered orally in comparison with placebo or other opioids (e.g., methadone, oxycodone, hydromorphone, fentanyl, and buprenorphine also in the transdermal mode of administration) written in English.

Exclusion criteria

Studies dealing with the use of morphine for breakthrough pain management were excluded.

Population

See **Results** section.

Interventions

Modified-release morphine v transdermal fentanyl
Modified-release morphine v modified-release oxycodone

<p>Outcomes Efficacy, side effects.</p>
<p>Results The authors aimed to do a meta-analysis, but did not find that the data were compatible with this aim. The results of the relevant (for the present purposes) included studies reporting data not elsewhere included in this evidence review are therefore reported narratively:</p> <p>- <u>Ahmedzai et al. (1997)</u>: Comparator: Modified-release morphine v transdermal fentanyl (cross-over trial). N = 202, previous opioid treatment (WHO ladder) = III. Study limitations: No allocation concealment, large losses to follow up. Drop-out rate = 45%. Reported efficacy: Not evidence of difference. Side effects: See evidence table for Tassanari et al. (2008).</p> <p>- <u>Lauretti et al. (2003)</u>: Comparator: Modified-release morphine v modified-release oxycodone (double-blind cross-over trial). N = 26, previous opioid treatment (WHO ladder) = II (tramadol). Study limitations: None listed. Drop-out rate = 15%. Reported efficacy: Not evidence of difference. Side effects: Morphine > nausea & vomiting.</p>
<p>General comments Comprehensive explicit search strategy Separately screening and assessment for inclusion by 2 review authors</p>
<p>References of Included Studies (For systematic reviews):</p> <p>- Ahmedzai, S., Brooks, D., on behalf of the TTS-Fentanyl Comparative Trial Group. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: Preference, efficacy and quality of life. <i>J Pain Symptom Manage</i> 13, 254-61. 1997.</p> <p>- Lauretti, G.R., Oliveira, G.M. and Pereira, N.L. Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. <i>Br J Cancer</i> 89: 2027–2030. 2003.</p>
<p>Citation: Reid, C. M., Martin, R. M., Sterne, J. A. C., Davies, A. N., and Hanks, G. W. Oxycodone for cancer-related pain - Meta-analysis of randomized controlled trials. <i>Archives of Internal Medicine</i> 166[8], 837-843. 2006.</p>
<p>Design: Systematic review w/ meta-analysis Country: United Kingdom Aim: To evaluate the efficacy and tolerability of oxycodone in cancer-related pain,</p>
<p>Inclusion criteria RCTs comparing oxycodone with placebo or an active analgesic drug in patients with cancer-related pain. All routes of drug administration and all formulations of oxycodone were considered.</p>
<p>Exclusion criteria Studies of combination oxycodone preparations (eg, oxycodone and acetaminophen).</p>
<p>Population 6 RCTs, 2 of which were not included in the meta-analysis (which is not a problem for the present purposes as 1 of them, Kalso & Vainio (1990), used immediate-release preparations and the other (Beaver et al., 1978) compared intramuscular preparations.</p> <p><u>The remaining 4 RCTs (all lasting from 10-20 days) were:</u></p> <p>- <u>Bruera et al. (1998)</u>: Double-blind cross-over study of patients with stable cancer pain (≥ 3 d of stable opioid doses). Number of patients entered/completed and withdrawals: 32/23, 9 Withdrawals of which 5 were due to adverse events (3 with morphine; 2 with oxycodone) and 4 for other reasons. Intervention: 7 d of each drug (crossover day 8), dose adjustments permitted until pain control achieved, rescue dose, 10% of 24-h dose, dose titration similar in both groups, mean morphine dosage = 72.6 mg every 12 h; mean oxycodone dosage = 46.5 mg every 12 h. Median morphine-oxycodone ratio = 1.5. Outcomes reported: Pain measured on VAS (10 cm) and CAT (0-4), no significant difference in pain intensity scores between treatments, no statistically significant differences in mean severity of any adverse events or in patient preference. Notes: Funded by pharmaceutical company.</p> <p>- <u>Hagen & Babul (1997)</u>: <i>Controlled-release hydromorphone v controlled-release oxycodone</i>: Double-blind crossover study of patients with chronic stable cancer pain (≥ 3 d of stable opioid doses; mean age = 56 years). Number of patients entered/completed and withdrawals: 44/31, 13 Withdrawals, of which 8 were due to adverse events (6 with oxycodone; 2 with hydromorphone) and 5 for other reasons. Interventions: 7 d of each drug (crossover day 8), dose adjustments permitted until pain control achieved, rescue dose = 10% of 24-h dose, dose titration similar in both groups, mean hydromorphone dosage = 30 mg per 24 h; mean oxycodone dosage = 124 mg per 24 h, hydromorphone-oxycodone ratio = 1.6. Outcomes reported: Pain measured on VAS (10 cm) and 5-point CAT (0-4), overall mean pain intensity across all days: VAS = 28 mm (CR oxycodone) and 31 mm (CR hydromorphone) ($p = .1$), CAT = 1.4 (CR oxycodone) and 1.5 (CR hydromorphone) ($p = .10$), nausea and sedation measured on 10-cm VAS, no significant differences in nausea or sedation scores or patient preference between groups. Notes: Funded by pharmaceutical company.</p>

- Heiskanen & Kalso (1997): Double-blind cross-over study of patients with chronic stable cancer pain (mean age = 60 years). Number of patients entered/completed and withdrawals: 45/27, 18 withdrawals, of which 7 were due to adverse events (5 with oxycodone; 2 with morphine) and 11 for other reasons. Intervention: Initial open-label dose titration phase until 48 h of effective pain relief, followed by crossover sequences lasting 3-6 d, rescue dosage, 1/6 to 1/8 of 24-h dose, dose titration similar in both groups, mean morphine dosage = 180 mg in 24 h, mean oxycodone dosage = 123 mg in 24 h, morphine-oxycodone ratio = 1.5. Outcomes reported: Pain measured on 4-point verbal rating scale, when stable phases were combined, pain control was better with CR morphine than with CR oxycodone, constipation was more common with oxycodone, vomiting with morphine, night time acceptability was better in morphine group. Notes: Assistance from Pharmaceutical company.

- Mucci-LaRusso et al. (1998): Double-blind parallel group of patients with chronic cancer pain requiring 30 to 340 mg of oxycodone or equivalent (mean age = 59 years). Number of patients entered/completed and withdrawals: 101/79, 21 withdrawals, of which 9 were due to adverse events (3 with oxycodone and 6 with morphine), 12 for other reasons (1 patient did not receive any medication). Intervention: Initial doses of study medication calculated from prestudy opioid requirements, dose titrated up until stable pain control for 48 h Dose titration similar in both groups, mean morphine dosage = 140 mg in 24 h, mean oxycodone dosage = 101 mg in 24 h, rescue dose = 1/6-1/8 of 24-h dose, morphine-oxycodone ratio = 1.4. Outcomes reported: Pain on 4-point CAT (0-3), pain scores from last 48 h of study used in efficacy analyses, reduction in mean pain scores of 0.6 from baseline in both groups, no statistically significant difference between treatments noted, no difference in quality of life scores or patient preference between groups. Notes: Funded by pharmaceutical company.

Interventions

Controlled-release morphine v controlled-release oxycodone

Controlled-release hydromorphone v controlled-release oxycodone

Outcomes

Pain intensity, adverse events

Results

Pain intensity: Controlled-release morphine v controlled-release oxycodone (meta-analysis):

Standardised weighted mean differences (WMD) = 0.20 (95% CIO -0.04 – 0.44, non-significant; $I^2 = 0\%$)

See also the **Population** section above for information on the results of the individual studies.

Adverse events: Controlled-release morphine/hydromorphone v controlled-release oxycodone (meta-analysis):

- Nausea: Odds ratio (OR) = 0.75 (95% CI 0.51-1.1), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing nausea on oxycodone = 53% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), 42% (Mucci-LaRusso et al., 1998) and 64% (Hagen & Babul, 1997), and percentage of study completers experiencing nausea on morphine = 53% (Heiskanen & Kalso, 1997), 74% (Bruera et al., 1998), and 48% (Mucci-LaRusso et al., 1998) and on hydromorphone 68% (Hagen & Babul, 1997).

- Constipation: OR = 1.22 (95% CI 0.76-1.95), non-significant, $I^2 = 39\%$. Percentage of study completers experiencing constipation on oxycodone = 53% (Heiskanen & Kalso, 1997), 70% (Bruera et al., 1998), 35% (Mucci-LaRusso et al., 1998) and 74% (Hagen & Babul, 1997), and percentage of study completers experiencing constipation on morphine = 49% (Heiskanen & Kalso, 1997), 70% (Bruera et al., 1998), and 21% (Mucci-LaRusso et al., 1998) and on hydromorphone 61% (Hagen & Babul, 1997).

- Drowsiness (excluding hydromorphone trial): OR = 0.72 (95% CI 0.47-1.1), non-significant, $I^2 = \text{NR}$. Percentage of study completers experiencing drowsiness on oxycodone = 49% (Heiskanen & Kalso, 1997), 87% (Bruera et al., 1998), and 31% (Mucci-LaRusso et al., 1998), and percentage of study completers experiencing drowsiness on morphine = 57% (Heiskanen & Kalso, 1997), 87% (Bruera et al., 1998), and 31% (Mucci-LaRusso et al., 1998).

- Difficulty concentrating: OR = 0.93 (95% CI 0.72-1.21), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing difficulty concentrating on oxycodone = 4% (Heiskanen & Kalso, 1997), 52% (Bruera et al., 1998), NR (Mucci-LaRusso et al., 1998) and 58% (Hagen & Babul, 1997), and percentage of study completers experiencing difficulty concentrating on morphine = 4% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), and NR (Mucci-LaRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).

- Hallucinations: OR = 1.46 (95% CI 0.69-3.07), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing hallucinations on oxycodone = 0% (Heiskanen & Kalso, 1997), 30% (Bruera et al., 1998), 0% (Mucci-LaRusso et al., 1998) and 0% (Hagen & Babul, 1997), and percentage of study completers experiencing hallucinations on morphine = 0% (Heiskanen & Kalso, 1997), 17% (Bruera et al., 1998), and 4% (Mucci-LaRusso et al., 1998) and on hydromorphone 6% (Hagen & Babul, 1997).

- Dry mouth (excluding hydromorphone trial): **OR = 0.56 (95% CI 0.38-0.83), significant, but $I^2 = \text{NR}$** . Percentage of study completers experiencing dry mouth on oxycodone = 35% (Heiskanen & Kalso, 1997), 74% (Bruera et al., 1998), and 33% (Mucci-LaRusso et al., 1998), and percentage of study completers experiencing dry mouth on morphine = 47% (Heiskanen & Kalso, 1997), 83% (Bruera et al., 1998), and 48% (Mucci-LaRusso et al., 1998).

- Vomiting: OR = 0.72 (95% CI 0.49-1.06), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing vomiting on oxycodone = 31% (Heiskanen & Kalso, 1997), 9% (Bruera et al., 1998), 0% (Mucci-LaRusso et al., 1998) and 26% (Hagen & Babul, 1997), and percentage of study completers experiencing vomiting on morphine = 35% (Heiskanen & Kalso, 1997), 22% (Bruera et al., 1998), and 2% (Mucci-LaRusso et al., 1998) and on hydromorphone 29% (Hagen & Babul, 1997).

- Agitation: OR = 1.12 (95% CI 0.78-1.61), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing agitation on oxycodone = 0% (Heiskanen & Kalso, 1997), 70% (Bruera et al., 1998), NR (Mucci-LaRusso et al., 1998) and 32% (Hagen & Babul, 1997), and percentage of study completers experiencing agitation on morphine = 2% (Heiskanen & Kalso, 1997), 52% (Bruera et al., 1998), and NR (Mucci-LaRusso et al., 1998) and on hydromorphone 32% (Hagen & Babul, 1997).

- **Dizziness:** OR = 0.89 (95% CI 0.48-1.66), non-significant, $I^2 = 63\%$. Percentage of study completers experiencing dizziness on oxycodone = 20% (Heiskanen & Kalso, 1997), 39% (Bruera et al., 1998), 21% (Mucci-LoRusso et al., 1998) and 35% (Hagen & Babul, 1997), and percentage of study completers experiencing dizziness on morphine = 24% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), and 31% (Mucci-LoRusso et al., 1998) and on hydromorphone 26% (Hagen & Babul, 1997).

- **Poor sleep:** OR = 0.79 (95% CI 0.42-1.48), non-significant, $I^2 = 27\%$. Percentage of study completers experiencing poor sleep on oxycodone = 0% (Heiskanen & Kalso, 1997), 65% (Bruera et al., 1998), 2% (Mucci-LoRusso et al., 1998) and 39% (Hagen & Babul, 1997), and percentage of study completers experiencing poor sleep on morphine = 0% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), and 2% (Mucci-LoRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).

- **Twitching:** OR not estimable because no individuals had discordant adverse effects. Percentage of study completers experiencing twitching on oxycodone = 2% (Heiskanen & Kalso, 1997), 48% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 29% (Hagen & Babul, 1997), and percentage of study completers experiencing twitching on morphine = 2% (Heiskanen & Kalso, 1997), 35% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 29% (Hagen & Babul, 1997).

- **Fatigue:** OR = 0.92 (95% CI 0.54-1.58), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing fatigue on oxycodone = 2% (Heiskanen & Kalso, 1997), 83% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 77% (Hagen & Babul, 1997), and percentage of study completers experiencing fatigue on morphine = 0% (Heiskanen & Kalso, 1997), 83% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).

- **Itch:** OR = 1.12 (95% CI 0.8-1.56), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing itch on oxycodone = 22% (Heiskanen & Kalso, 1997), 35% (Bruera et al., 1998), 20% (Mucci-LoRusso et al., 1998) and 55% (Hagen & Babul, 1997), and percentage of study completers experiencing itch on morphine = 24% (Heiskanen & Kalso, 1997), 43% (Bruera et al., 1998), and 21% (Mucci-LoRusso et al., 1998) and on hydromorphone 45% (Hagen & Babul, 1997).

- **Vivid dreams:** OR = 1.21 (95% CI 0.65-2.27), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing vivid dreams on oxycodone = 2% (Heiskanen & Kalso, 1997), 26% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 39% (Hagen & Babul, 1997), and percentage of study completers experiencing vivid dreams on morphine = 0% (Heiskanen & Kalso, 1997), 22% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 32% (Hagen & Babul, 1997).

- **Headache:** OR = 0.93 (95% CI 0.51-1.68), non-significant, $I^2 = 22\%$. Percentage of study completers experiencing headache on oxycodone = 4% (Heiskanen & Kalso, 1997), 43% (Bruera et al., 1998), 10% (Mucci-LoRusso et al., 1998) and 39% (Hagen & Babul, 1997), and percentage of study completers experiencing headache on morphine = 4% (Heiskanen & Kalso, 1997), 30% (Bruera et al., 1998), and 6% (Mucci-LoRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).

- **Sweating:** OR = 1.05 (95% CI 0.71-1.56), non-significant, $I^2 = 0\%$. Percentage of study completers experiencing sweating on oxycodone = 35% (Heiskanen & Kalso, 1997), 61% (Bruera et al., 1998), 4% (Mucci-LoRusso et al., 1998) and 55% (Hagen & Babul, 1997), and percentage of study completers experiencing sweating on morphine = 31% (Heiskanen & Kalso, 1997), 48% (Bruera et al., 1998), and 4% (Mucci-LoRusso et al., 1998) and on hydromorphone 61% (Hagen & Babul, 1997).

General comments

Comprehensive search conducted

The full-text versions of potentially eligible articles independently assessed by 2 of the investigators

Independent data extraction from included trials by 2 authors

Quality of included studies not high

Vast majority of adverse events analyses includes hydromorphone trial

Not first-line in all patients

References of Included Studies (For systematic reviews):

- Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. II: comparisons of intramuscular oxycodone with intramuscular morphine and codeine. *J Pharmacol Exp Ther*. 1978;207:101-108.

- Bruera E, Belzile M, Pituskin E, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J Clin Oncol*. 1998;16: 3222-3229.

- Hagen NA, Babul N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. *Cancer*. 1997;79:1428-1437.

- Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. *Pain*. 1997;73:37-45.

- Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther*. 1990;47:639-646.

- Mucci-LoRusso P, Berman B, Silberstein P, et al. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain. *Eur J Pain*. 1998;2:239-249.

Citation: Tassinari, D., Sartori, S., Tamburini, E., Scarpi, E, Raffaelli, W., Tombesi, P., & Maltoni, M. (2008). Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: A meta-analysis and systematic review of the literature. *Journal of Palliative Medicine*, 11, 492-501.

Design: Systematic review w/ meta-analysis

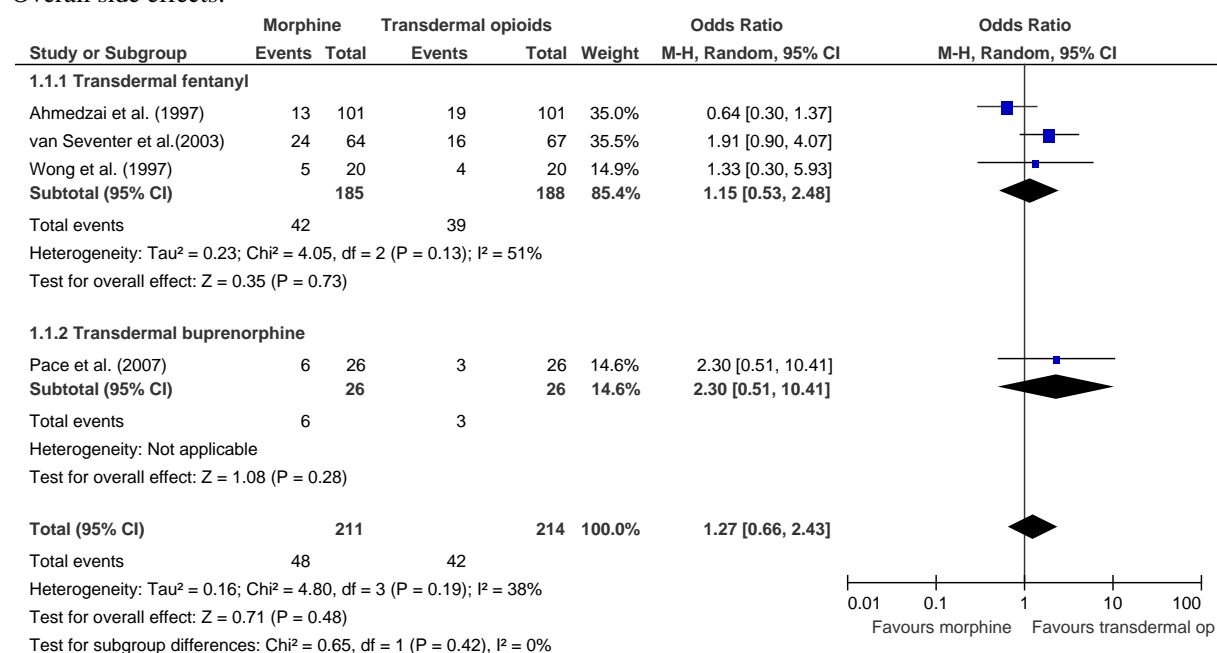
Country: Italy

<p>Aim: To assess the adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison with slow release oral morphine.</p>				
<p>Inclusion criteria Phase 3 RCTs comparing slow-release morphine to transdermal opiates in patients with moderate-severe cancer pain with a defined need for opiates at the time of entering the trial</p>				
<p>Exclusion criteria Randomised phase 2 trials, trials comparing the outcomes with a historical arm or literature data, trials with patients with non-cancer pain, trials not reporting safety data or not reporting adequate information about randomisation process in methods/results section, trials including patients treated with analgesic approaches other than morphine or transdermal opiates, and trials including patients needing an opiate titration at the time of entering the trial.</p>				
<p>Population 4 RCTs: <u>Transdermal fentanyl v slow-release morphine:</u> - Ahmedzai et al. (1997): N = 202; randomised cross-over trial using ‘oral morphine 1 mg/transdermal fentanyl 10 µg’ ratio as equianalgesic doses of patients; Jadad score = 3 (moderate quality). - van Seventer et al. (2003): N = 131; fentanyl daily dose = 600 µg v morphine daily dose = 60 mg; Jadad score = 3 (moderate quality). - Wong et al. (1997): N = 47; fentanyl daily dose = 1260 ± 183 µg v morphine daily dose = 137 ± 18.3 mg; Jadad score = 2 (low quality). <u>Transdermal buprenorphine v slow-release morphine:</u> - Pace et al. (2007): N = 52; buprenorphine daily dose = 840 µg v morphine daily dose = 60 mg; Jadad score = 2 (low quality).</p>				
<p>Interventions Transdermal fentanyl v slow-release morphine Transdermal buprenorphine v slow-release morphine</p>				
<p>Outcomes Overall adverse effects, overall neurological (insomnia, drowsiness, confusion, headache and vertigo) and gastrointestinal (constipation, diarrhea, anorexia, nausea, vomiting and itching) adverse effects, constipation, nausea, drowsiness, patients’ preference and trial withdrawal.</p>				
<p>Results Meta-analyses were performed based on the data extracted by Tassinari et al. (2008), but subgrouped by type of transdermal opioid, which constituted analyses not reported by Tassinari et al. (2008).</p> <p>The table below lists the results of the analyses (see also the forest plots below for more detail). From the table and the forest plots it is evident that the treatments did not differ significantly in terms of any of the side effects apart from the following where the transdermal option was favoured in each case: Overall gastrointestinal side effects (buprenorphine treatment only), constipation (fentanyl and buprenorphine) and patient preference (fentanyl only).</p>				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Overall side effects	4	425	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.66, 2.43]
1.1.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.53, 2.48]
1.1.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	2.30 [0.51, 10.41]
1.2 Overall gastrointestinal side effects	4	425	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.66, 3.08]
1.2.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.56, 2.05]
1.2.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	4.79 [1.14, 20.21]
1.3 Nausea	4	425	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.57, 2.36]
1.3.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]

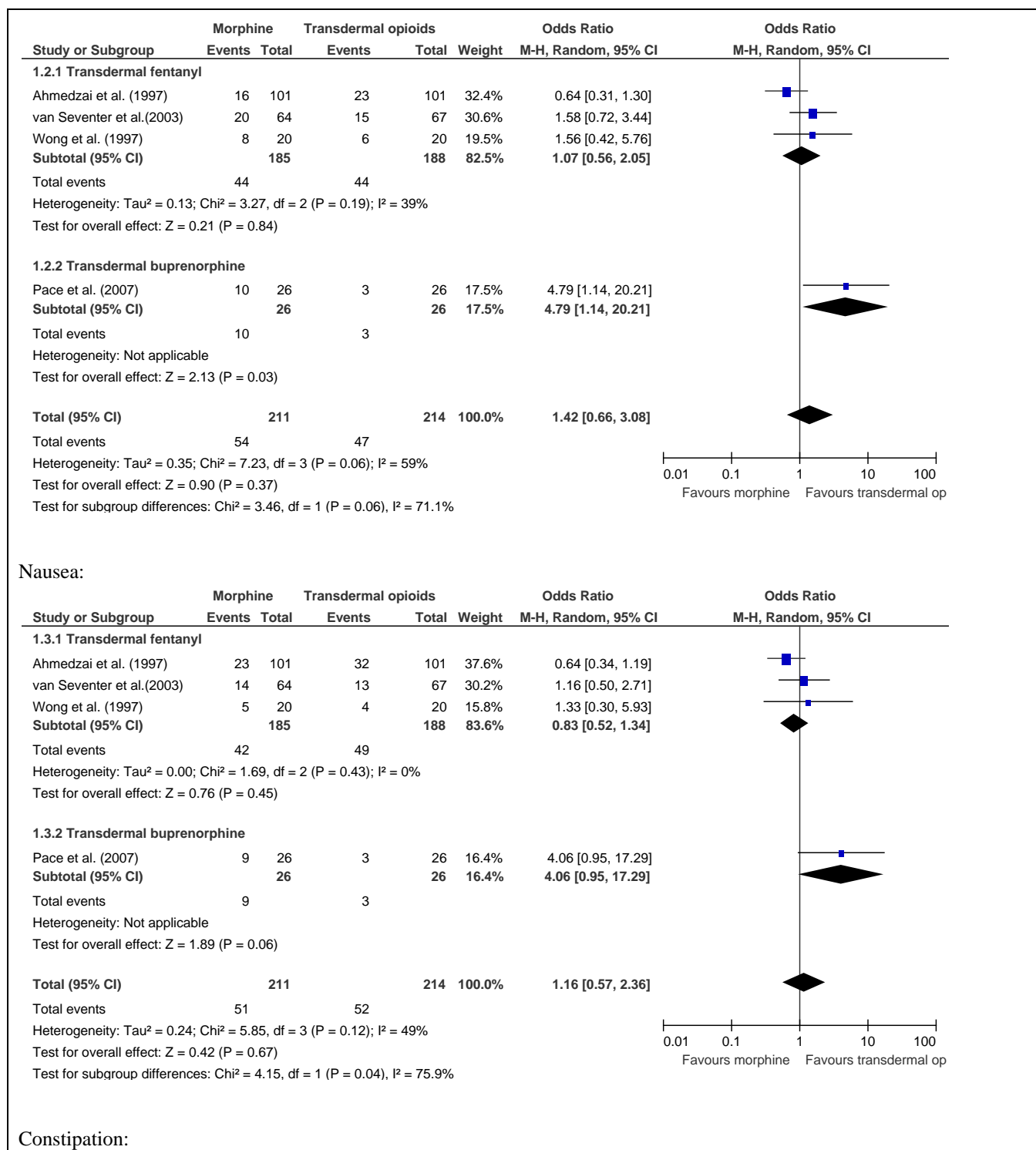
1.3.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	4.06 [0.95, 17.29]
1.4 Constipation	4	425	Odds Ratio (M-H, Random, 95% CI)	2.63 [1.57, 4.39]
1.4.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	2.35 [1.37, 4.03]
1.4.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	7.50 [1.45, 38.85]
1.5 Overall neurological side effects	4	425	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.95, 3.10]
1.5.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.67 [0.78, 3.57]
1.5.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.39, 8.59]
1.6 Drowsiness	4	425	Odds Ratio (M-H, Random, 95% CI)	1.58 [0.81, 3.06]
1.6.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.75 [0.85, 3.59]
1.6.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.10, 4.18]
1.7 Patient preference	3	373	Odds Ratio (M-H, Random, 95% CI)	2.32 [1.19, 4.54]
1.7.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	2.32 [1.19, 4.54]
1.8 Hypoventilation	2	242	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.30]
1.8.1 Transdermal fentanyl	2	242	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.30]

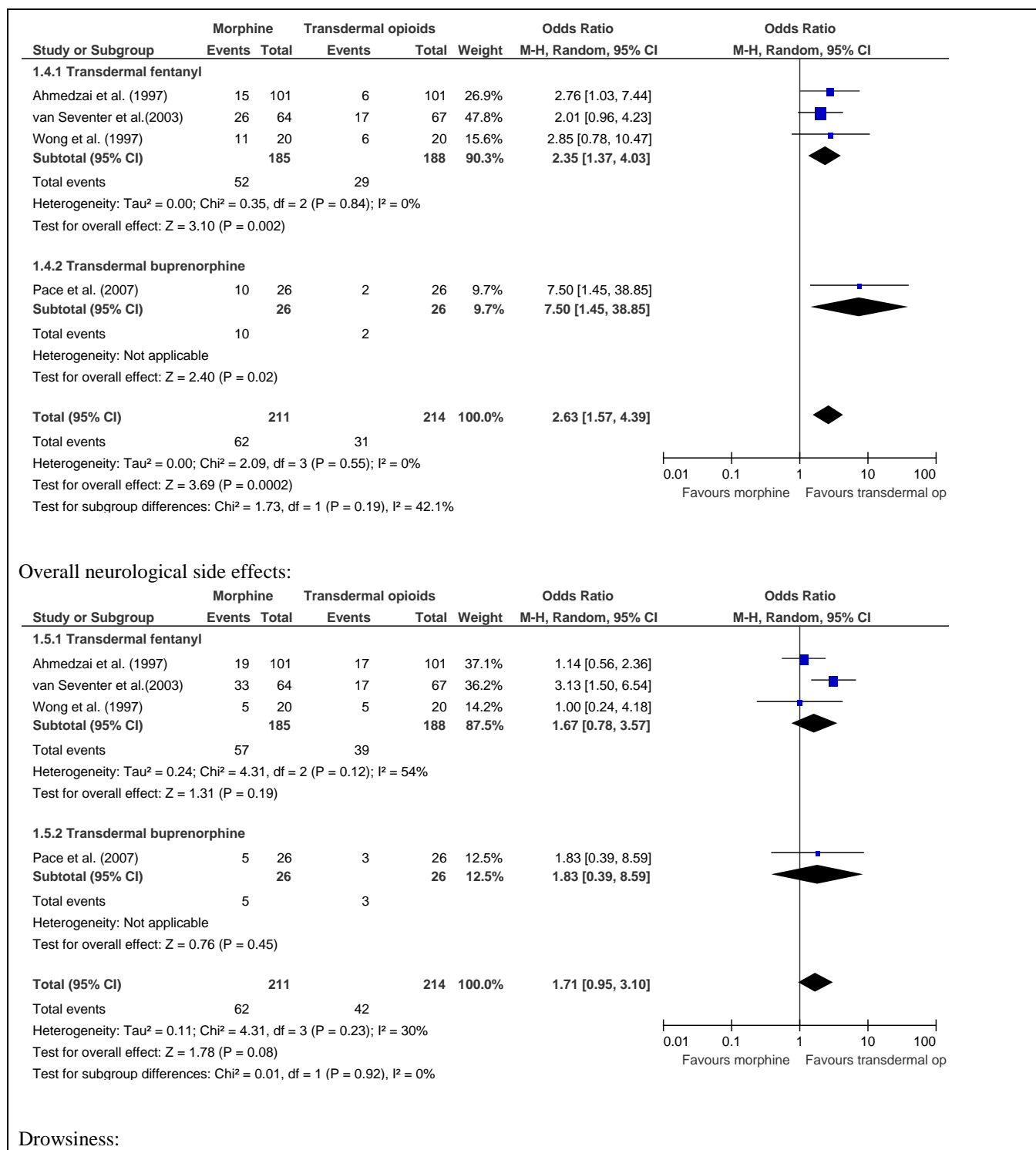
Trial withdrawal and changes in opiate treatment was reported in 2 trials (not reported which 2 trials) and heterogeneity was found for both of these outcomes ($p < 0.001$ and $p = 0.008$, respectively; ORs = 0.62, $p = 0.59$; and OR = 0.575, $p = 0.607$, respectively)

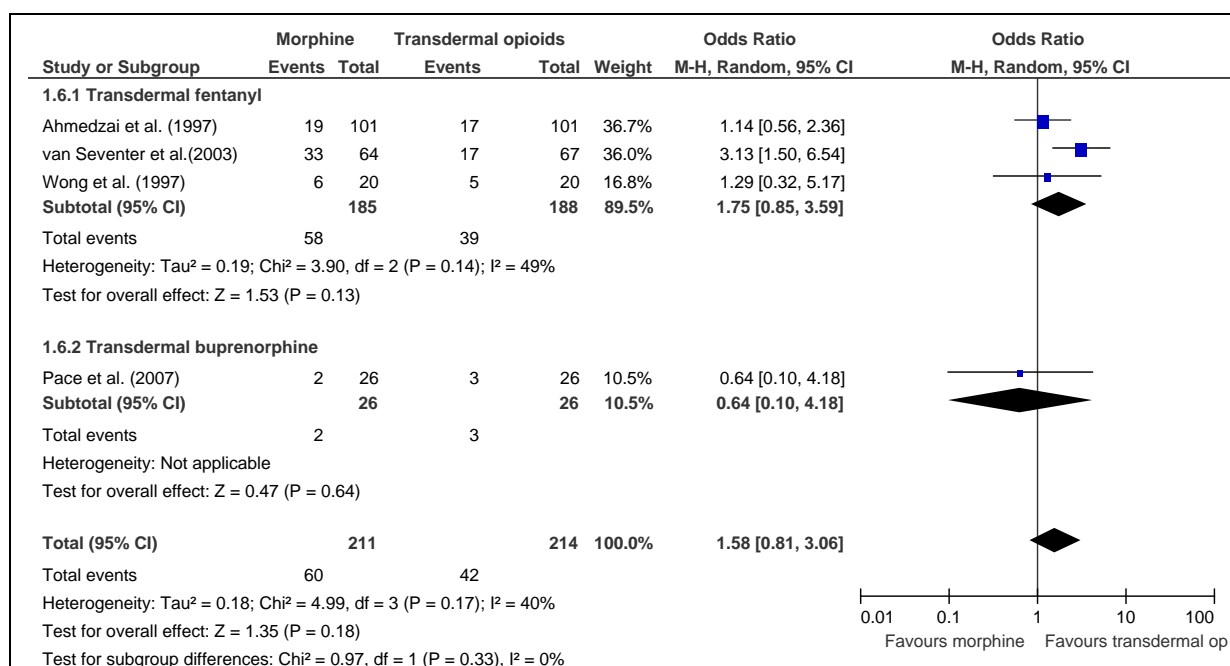
Overall side effects:



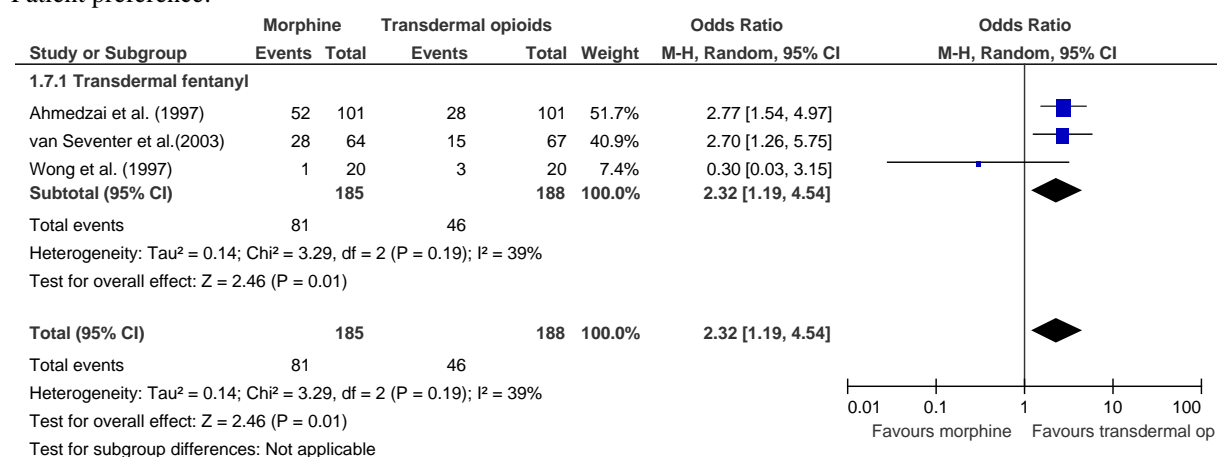
Overall gastrointestinal side effects:



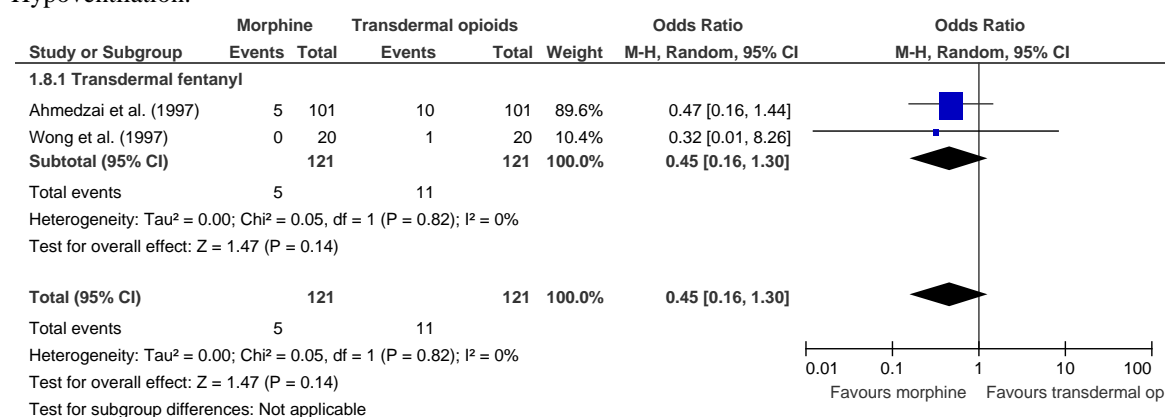




Patient preference:



Hypoventilation:



General comments

Systematic search of MEDLINE and EMBASE from 1966-2006, performed independently by 2 authors

Selected trials were independently assigned a JADAD score by 2 authors

Heterogeneity reported

Not first-line treatment in all the studies

References of Included Studies (For systematic reviews):

- Ahmedzai, S., Brooks, D., on behalf of the TTS-Fentanyl Comparative Trial Group. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: Preference, efficacy and quality of life. *J Pain Symptom Manage* 13, 254-61. 1997.
- Pace, M. C., Passavanti, M. B., Grella, E., Mazzariello, L., Maisto, M., Barbarisi, M., Baccari, E., Sansone, P., Aurilio, C., Pace, Maria Caterina, Passavanti, Maria Beatrice, Grella, Elisa, Mazzariello, Luigi, Maisto, Massimo, Barbarisi, Manlio, Baccari, Ena, Sansone, Pasquale, and Aurilio, Caterina. Buprenorphine in long-term control of chronic pain in cancer patients. *Frontiers in Bioscience* 12, 1291-1299. 2007.
- van, Seventer R., Smit, J. M., Schipper, R. M., Wicks, M. A., and Zuurmond, W. W. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. *SO: Current medical research and opinion* 19[6], 457-469. 2003.
- Wong J.O., Chiu, G.L., Tsao, C.J., et al. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anaesthesiol Sinica* 35, 25-32. 1997.

Citation: Zuurmond, W. W. & Davis, C. Safety and efficacy of transdermal fentanyl (Durogesic) compared with sustained-release morphine in patients with cancer pain [abstract]. *SO: Proceedings of the American Society of Clinical Oncology* 21 (Pt 1), 377a, Abstract. 2002.

Design: Abstract on the pooled analysis of two open randomised parallel 4-week studies

Country: Europe

Aim: to compare the safety and efficacy of transdermal fentanyl with sustained release morphine (SRM), in the treatment of strong-opioid-naïve patients, and patients transferring from weak to strong opioids, with chronic cancer pain.

Inclusion criteria

Not reported

Exclusion criteria

Not reported

Population

Not reported

Interventions

Transdermal fentanyl: Transdermal fentanyl was prescribed the lowest dose, 25 µg/h patch every 72 hours, with incremental titration of 25 µg/h to achieve adequate pain control.

Sustained-release morphine: Starting dose of 30 mg sustained-release morphine 12 hourly.

Outcomes

Constipation, pain control, drowsiness, sleep quality and overall patient satisfaction with treatment.

Results

- At day 7, significantly more patients were constipated in the sustained-release morphine group compared with the transdermal fentanyl group ($p = 0.002$).
- Pain control: Sustained-release morphine = transdermal fentanyl
- Side effects: Transdermal fentanyl < sustained-release morphine ($p=0.01$)
- Convenience of use: Transdermal fentanyl > sustained-release morphine ($p=0.01$)
- Overall impression: Transdermal fentanyl = sustained-release morphine ($p=0.06$)
- Compared to baseline, at the end of study transdermal fentanyl patients suffered significantly less ($p=0.02$) from troublesome side effects compared to patients treated with sustained-release morphine.
- More patients treated with sustained-release morphine withdrew from the study due to adverse events compared to the transdermal fentanyl group [but it is not reported whether this is numerically more or significantly more patients].

General comments

These data are only published in abstract form and it is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

References of Included Studies (For systematic reviews): NA

3.5 First-line treatment if oral opioids are not suitable – transdermal patches

2c: Are fentanyl patches more effective than buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral treatment is not suitable?

Evidence tables 4

Citation: Sarhan T, & Doghem M. A comparison of two trans-dermal drug delivery systems; Buprenorphine and fentanyl for chronic cancer pain management. European Journal of Pain Conference[var.pagings], September. 2009.
Design: RCT (parallel groups; abstract only) Country: Egypt Aim: To compare three escalating doses of transdermal fentanyl and transdermal buprenorphine for chronic cancer pain management.
Inclusion criteria None reported
Exclusion criteria None reported
Population N = 32 opioid naive patients suffering from chronic cancer pain with visual analogue scale (VAS) ≥ 7 , randomly allocated into one of two groups with N = 16 patients each
Interventions <u>Fentanyl:</u> Transdermal fentanyl patches every 3 days starting with 25 µg/h escalated to 50 µg/h and then gradually to 75 µg/h patch for VAS ≤ 3 . <u>Buprenorphine:</u> Buprenorphine trans-dermal opioid patches starting with a doses of 35 µg/h, increased to 52.5µg/h patch and gradually to 70 µg/h for VAS ≤ 3 .
Outcomes Severity of pain by VAS (every 3 days), mean number of each category patch dose, treatment satisfaction, mean daily dose of diclofenac sodium, mean cost of treatment, side effects and complications. Measured for 6 weeks.
Results No statistically significant differences in the mean VAS and other measurements before and for 6 weeks of treatment between (?) the groups. Drowsiness and local skin complication: Buprenorphine > fentanyl
General comments - Random allocation - Measurements done by an assessor blinded to the study - These data are only published in abstract form and it is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

Citation: Wirz S, Wittmann M, Schenk M, Schroeck A, Schaefer N, Mueller M, Standop J, Kloecker N, Nadstawek J. (2009). Gastrointestinal symptoms under opioid therapy: A prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine. European Journal of Pain 13; 737-43.
Design: Prospective controlled trial Country: Germany Aim: To evaluate the effect of long-term treatment with oral sustained-release hydromorphone, transdermal fentanyl and transdermal buprenorphine on nausea, emesis and constipation. <i>Only data pertaining to the comparison between transdermal fentanyl and transdermal buprenorphine [as outlined in the PICO] will be reported.</i>
Inclusion criteria <i>Patients were randomly selected</i> “After identifying outpatients undergoing pain therapy consisting of one of the study medications, patients were selected for participation by a computer generated random selection scheme. In accordance with the requirements of the local ethics committee, we first selected patients by randomly and then asked them to participate after giving their informed consent.

To avoid opioid-naïve patients being enrolled, only patients who had already taken one of the study medications for longer than 4 weeks were included. After the enrolment of 62 patients per group the study was finalised.” Page 738

Patients with cancer related pain, pure nociceptive pain, opioid therapy with one of the study medications for longer than 28 days, strictly ambulatory treatment, the patient’s cooperation, and a score of 0–3 on the ECOG Performance Status scale.

Exclusion criteria

Referral for inpatient treatment diarrhoea and diseases that are likely to cause diarrhoea (e.g. carcinoma of the pancreas), neuropathic or mixed pain, breakthrough pain, severe incidental pain (NRS > 5), communication deficits, hepatic or renal impairment with the risk of accumulation, conditions likely to interfere with transdermal or oral administration or with drug absorption, current chemotherapy, radiotherapy, immobilization or inability to walk, entering the terminal phase, infections, prior history of drug addiction or alcohol abuse, and concomitant treatment with other opioid analgesics during the study period. Modification of the dose of study opioids was a particular reason for exclusion.

Population

Fentanyl: N = 55 randomly selected patients; mean age = 64.1 (SD = 11.6) years; 28 males; mean ECOG score = 2.1 (SD = 1.3); mean EORTC item 1 = 3 (SD = 1.2); mean EORTC item 2 = 3 (SD = 1.1); mean EORTC item 3 = 2.5 (SD = 1.2); mean EORTC item 4 = 2.4 (SD = 1.4); mean EORTC item 5 = 1.6 (SD = 1); mean pain at rest = 2.8 (SD = 2.8); mean duration of opioid use = 206.9 (SD = 291.2) days; mean morphine equivalent (1:100) opioid daily dose = 183.3 (SD = 131.74) mg; use of dipyrone: N = 26; use of NSAIDs: N = 14; Patients with a constipating medication: N = 28; Amitriptyline: N = 4 (mean = 31.3 (SD = 12.5) mg/d); Verapamil: N = 0; Nifedipine: N = 0; Furosemide: N = 7 (mean = 33.3 (SD = 11.5) mg); Pantoprazole: N = 24 (mean = 47.1 (SD = 21) mg); Antiemetics (except metoclopramide): N = 16; Haloperidol: N = 4 (mean = 1.9 (SD = 1.2) mg/d); Promethazine: N = 2 (mean = 17.5 (SD = 10.6) mg); Dimenhydramine: N = 1 (mean = 25 mg/d); Ondansetron: N = 0; hypertension: N = 5; mild coronary heart disease: N = 2; pulmonary diseases: N = 4; history of cardiac arrhythmia: N = 0. Renal or hepatic impairment: N = 0. Transmucosal fentanyl: N = 5.

Buprenorphine: N = 61 randomly selected patients; mean age = 65.3 (SD = 10.7) years; 36 males; mean ECOG score = 1.9 (SD = .8); mean EORTC item 1 = 3.5 (SD = .8); mean EORTC item 2 = 3.4 (SD = .7); mean EORTC item 3 = 2.2 (SD = 1); mean EORTC item 4 = 2.2 (SD = .9); mean EORTC item 5 = 1.4 (SD = .8); mean pain at rest = 3 (SD = 2.3); mean duration of opioid use = 174.1 (SD = 222.5) days; mean morphine equivalent (1:75) opioid daily dose = 88.52 (SD = 39.8) mg; use of dipyrone: N = 23; use of NSAIDs: N = 14; Patients with a constipating medication: N = 28; Amitriptyline: N = 10 (mean = 30 (SD = 10.5) mg/d); Verapamil: N = 2 (mean = 170 (SD = 14.1) mg/d); Nifedipine: N = 3 (mean = 20 (SD = 0) mg/d); Furosemide: N = 8 (mean = 20 mg); Pantoprazole: N = 15 (mean = 34.5 (SD = 20.9) mg); Antiemetics (except metoclopramide): N = 12; Haloperidol: N = 0; Promethazine: N = 0; Dimenhydramine: N = 1 (mean = 50 mg/d); Ondansetron: N = 0; hypertension: N = 4; mild coronary heart disease: N = 6; pulmonary diseases: N = 1; history of cardiac arrhythmia: N = 2. Renal or hepatic impairment: N = 0. Sublingual buprenorphine: N = 5.

Interventions

Transdermal fentanyl v transdermal buprenorphine

If necessary, fast-acting formulations of the same drug were allowed (transdermal fentanyl group: 200 lg transmucosal fentanyl, transdermal buprenorphine group: 0.2 mg sublingual buprenorphine). No opioids other than the study opioids were permitted during the course of the study. No variation was allowed during the course of the observation period.

Outcomes

The occurrence of stool free periods >72 h, constipation, nausea, emesis, medication for symptom control, the use of analgesics and co-analgesics. The intensity of pain at rest, the intensity of nausea, and constipation was assessed once daily using the numerical rating scale (NRS, 0–10, 0 = no symptom, 10 = worst symptom imaginable). Patient mobility assessed by the ECOG Performance Status scale and items 1–5 of the EORTC questionnaire (EORTC QLQ 30, version 3) (1: not at all, 2: a little, 3: quite a bit, 4: very much; Item 1 “Do you have trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?” Item 2 “Do you have any trouble taking a long walk?” Item 3 “Do you have any trouble taking a short walk out of the house?” Item 4 “Do you need to stay in bed or in a chair during the day?” Item 5 “Do you need help with eating, dressing, washing yourself or using the toilet?”)

Results All of the statistical analyses performed by the authors were calculated on the present 2 groups and a third group of patients on oral hydromorphone using statistics appropriate for > 2 groups (such as ANOVA). These statistics are not reported as they are not targeted to the comparison of current interest.

- Constipation: Transdermal fentanyl: Mean = 2.4 (SD = 3); transdermal buprenorphine: Mean = 2.2 (SD = 2.7)
- EORTC constipation item: Transdermal fentanyl: Mean = 2.1 (SD = 1.3); transdermal buprenorphine: Mean = 2.3 (SD = 1.3)
- Mean defecation rate: Transdermal fentanyl: Mean = .7 (SD = .6) 1/day; transdermal buprenorphine: Mean = .8 (SD = .6) 1/day
- Stool-free interval > 72 hours: Transdermal fentanyl: N = 12; transdermal buprenorphine: N = 13

- Use of laxatives: Transdermal fentanyl: N = 27; transdermal buprenorphine: N = 39
- Nausea: Transdermal fentanyl: Mean = 1.3 (SD = 2.2); transdermal buprenorphine: Mean = 1.2 (SD = 1.7)
- EORTC nausea item: Transdermal fentanyl: Mean = 1.8 (SD = 1.1); transdermal buprenorphine: Mean = 1.7 (SD = .9)
- Emesis: Transdermal fentanyl: Mean = .1 (SD = .3) 1/day, N = 9; transdermal buprenorphine: Mean = .1 (SD = .3) 1 day, N = 8
- EORTC emesis item: Transdermal fentanyl: Mean = 1.6 (SD = .9); transdermal buprenorphine: Mean = 1.4 (SD = .8)
- Use of anti-emetics: Transdermal fentanyl: N = 23; transdermal buprenorphine: N = 19
- Cumulative use of different substances: Transdermal fentanyl: N = 43; transdermal buprenorphine: N = 53
- Sodium picosulfate: Transdermal fentanyl: Mean = 11.5 (SD = 7.2) mg/day, N = 8; transdermal buprenorphine: Mean = 10 (SD = 0) mg/day, N = 9.
- Lactulose: Transdermal fentanyl: Mean = 18.8 (SD = 5.8) g/day, N = 11; transdermal buprenorphine: Mean = 16.3 (SD = 8.9) g/day, N = 9.
- Polyethylene glycol: Transdermal fentanyl: Mean = 20.7 (SD = 7.2) g/day, N = 12; transdermal buprenorphine: Mean = 21.8 (SD = 7) mg/day, N = 19.
- Paraffin: Transdermal fentanyl: N = 0; transdermal buprenorphine: N = 0.
- Bisacodyl: Transdermal fentanyl: N = 0; transdermal buprenorphine: Mean = 20 (SD = 14.1) mg/day, N = 2.
- **Metoclopramide**: Transdermal fentanyl: Mean = 22.5 (SD = 13.1) mg/day, N = 12; transdermal buprenorphine: Mean = 12.4 (SD = 6.5) mg/day, N = 14. *Doses are likely to be statistically significantly different between the groups.*

General comments

- Random selection of patients undergoing treatment with the target drugs, not random allocation to treatment
- Possible baseline differences
- The investigators checked daily whether the administration of all analgesics (opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants), and adjuvants (laxatives, antiemetics) had been continued at the same dose levels.
- Not first-line

3.6 First-line treatment if oral opioids are not suitable – subcutaneous delivery

2d: Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable?

No evidence was identified for this review question

3.7 First-line treatment if oral opioids are not suitable – transdermal patch versus subcutaneous delivery

2e: Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable?

No evidence was identified for this review question

3.8 First-line treatment for breakthrough pain in patients who can take oral opioids

2f: What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)?

Evidence table 5

<p>Citation: Davies, A., Sitte, T., Elsner, F., Reale, C., Espinosa, J., Brooks, D., and Fallon, M. Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain. <i>Journal of Pain and Symptom Management</i> 41[2], 358-366. 2011</p>
<p>Design: Multicenter, randomized, double-blind/double-dummy, crossover study Country: Europe and India Aim: To compare fentanyl pectin nasal spray (FPNS) to immediate-release morphine sulfate (IRMS) in patients with breakthrough cancer pain (BTCP).</p>
<p>Inclusion criteria Patients with a histologically confirmed diagnosis of cancer, who were receiving a fixed-schedule opioid regimen at a total daily dose ≥ 60 mg/day oral morphine for background cancer-related pain, and had one to four episodes per day of moderate-severe BTCP.</p>
<p>Exclusion criteria Patients with uncontrolled or rapidly escalating background pain or whose conditions were medically unstable, or with a past inability to tolerate fentanyl or other opioids and any disorder or medication use likely to adversely affect normal functioning of the nasal mucosa.</p>
<p>Population N = 110, mean age at baseline = 55.9 ± 12.3 years (median age = 57 years).</p>
<p>Interventions The study consisted of four phases: (1) Screening phase (maximum 10 days), (2) Open dose titration phase (maximum 14 days; used to identify an effective FPNS dose between 100-800 mg/episode of target BTCP. Patients had to complete the dose-titration phase (titration to an effective dose of FPNS that successfully treated two consecutive BTCP episodes without unacceptable adverse events) to progress to the next phase. (3) Double-blind/double-dummy treatment phase (3-21 days; in which up to 10 BTCP episodes were treated (five treated with FPNS and encapsulated oral placebo, five with IRMS and nasal spray placebo). For all episodes, patients were instructed to take the oral treatment just before the nasal treatment. IRMS dose was determined for each patient as one-sixth the total daily oral morphine dose equivalent of the patient's background opioid medication or the patient's previously identified "effective" dose of IRMS for BTCP.), (4) End-of-treatment phase (1-14 days after the last dose).</p>
<p>Outcomes Pain intensity (measured on an 11-point numeric scale at baseline and at 5, 10, 15, 30, 45 and 60 minutes after dosing). Pain relief (measured on a 5-point numeric scale at 5, 10, 15, 30, 45 and 60 minutes after dosing). Adverse events, nasal assessments, patient satisfaction.</p>
<p>Results - 106/110 patients enrolled in the open dose titration phase took study medication and were included in the safety population. - 84 patients identified an effective and tolerable FPNS dose during the titration phase and were randomly assigned to double-blind treatment. - 6 and 5 patients withdrew from the titration phase because of lack of efficacy and adverse events, respectively. 79/84 patients randomly assigned completed the study.</p> <p><u>Pain: Per-episode analysis (clinically meaningful pain relief defined as ≥ 2 point reduction in pain intensity):</u> - ≥ 2 point reduction in pain intensity (% of episodes): 5 min: FPNS (25.3%) = IRMS (22.8%); 10 min: FPNS (52.4%) > IRMS (45.4%); 15 min: FPNS (75.5%) > IRMS (69.3%); 30 min: FPNS (86.8%) = IRMS (82.9%); 45 min: FPNS (89.2%) = IRMS (88.6%); 60 min: FPNS (91.4%) = IRMS (89.4%). - Pain relief score ≥ 2: 5 min: FPNS (20.2%) = IRMS (20.1%); 10 min: FPNS (39.4%) = IRMS (34.8%); 15 min: FPNS</p>

(60.2%) > IRMS (53.4%); 30 min: FPNS (82.4%) > IRMS (71.4%); 45 min: FPNS (87.4%) = IRMS (83.4%); 60 min: FPNS (91.3%) = IRMS (87.4%).

- Max total pain relief $\geq 33\%$: FPNS = IRMS at 10 mins; **FPNS > IRMS at 15, 30, 45 and 60 mins, i.e., significantly more episodes achieved max total pain relief of $\geq 33\%$ after FPNS compared to IRMS.**

- Percentage of episodes requiring rescue medication: FPNS = IRMS

Patient acceptability (measured by 3 questions on 1-4 scale):

“How satisfied are you overall with the nasal spray you have used to treat this episode of BTCP?”:

“How satisfied are you with the speed of relief you gained with the nasal spray in the treatment of this episode of BTCP?”

“How satisfied are you with the reliability of the nasal spray you have used to treat this episode of BTCP?”

All 3 questions, the first 2 both at 30 and 60 mins and the latter at 60 mins, were rated more favourable for FPNS than for IRMS.

Adverse events and nasal tolerability:

- Treatment-emergent adverse events: 6 FPNS and 2 IRMS treatments (in 8 patients) resulted in discontinuation of study drug.

- No consistent patterns of reporting of nasal symptoms such as stuffy/blocked nose, runny nose, itching/sneezing, crusting/dryness of nose, burning/discomfort, nasal bleeding, cough, postnasal drip, sore throat, or taste disturbance and none of these nasal tolerability parameters were reported at an intensity of >2-3 (moderate or severe). FPNS = IRMS on all of these parameters.

General comments

- Double-blind/double-dummy controlled

- Modified intent-to-treat analysis including all patients in the randomized population who had treated at least one pain episode with each study medication (FPNS or IRMS) and had, for those episodes, a baseline and at least one subsequent pain intensity measurement. The safety population included all patients who had had ≥ 1 doses of FPNS.

- Drop-outs explained

- No correction for multiple analyses

References of Included Studies (For systematic reviews): NA

Citation: Vissers, D., Stam, W., Nolte, T., Lenre, M., Jansen, J., Vissers, Debby, Stam, Wiro, Nolte, Thomas, Lenre, Malin, and Jansen, Jeroen. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. *Current Medical Research & Opinion* 26[5], 1037-1045. 2010.

Design: Systematic review of RCTs w/ network meta-analysis

Country: International

Aim: To compare the efficacy of intranasal fentanyl spray (INFS), oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT) and immediate-release oral morphine (IRM) for the treatment of breakthrough cancer pain.

Inclusion criteria

RCTs on the management of breakthrough pain that allows comparison of INFS, FBT, OTFC and IRM in adult cancer patients suffering from breakthrough pain and treated with opioid analgesics for the management of background pain reporting pain intensity difference.

Exclusion criteria

None listed

Population

6 RCTs, 4 of which compared placebo to OTFC (Farrar et al., 1998), INFS (Kress et al., 2009), and FBT (Portenoy et al., 2006; Slatkin et al., 2007). The other 2 trials compared OTFC with IRM (Coluzzi et al., 2001 - *Also included in Zeppetella et al., 2009*) and INFS with OTFC (Mercadante et al., 2009).

The minimum episode frequency for inclusion in the INFS trials was 3 per week, and 1 for the other trials. The maximum episode frequency was 4 episodes per day for all trials. Pain intensity at the beginning of a breakthrough cancer pain episode and background opioid treatments were comparable across studies.

Coluzzi et al. (2001, also included in Zeppetella et al., 2009): N (double-blind phase) = 89; 47 males; mean age = 55 (SD = 11) years; number of treated episodes = NR for OTFC and IRM; mean pain intensity at time 0 = 6.9 for OFTC and 6.1 for IRM.

Farrar et al. (1998): N (double-blind phase) = 92; 41 males; mean age = 54 (SD = 12) years; number of treated episodes = 219 for placebo and 511 for OTFC; mean pain intensity at time 0 = 6 for placebo and 5.9 for OTFC.

Kress et al. (2009): N (double-blind phase) = 111; 56 males; mean age = 60.7 (SD = 9.1) years; number of treated episodes = 219 for placebo and 662 for INFS; mean pain intensity at time 0 = 6.4 (SD = 1.4) for placebo and 6.4 (SD = 1.3) for

<p>INFS.</p> <p><u>Mercadante et al. (2009)</u>: N (double-blind phase) = 139; 79 males; mean age = 62 (SD = 11.6) years; number of treated episodes = 577 for INFS and OTFC; mean pain intensity at time 0 = 6.4 (SD = 1.6) for INFS and 6.4 (SD = 1.5) for OTFC.</p> <p><u>Portenoy et al. (2006)</u>: N (double-blind phase) = 77; 42 males; mean age = 57.5 (SD = 13.6) years; number of treated episodes = 208 for placebo and 493 for FBT; mean pain intensity at time 0 = 6.9 (SD = 0.2) for placebo and for FBT.</p> <p><u>Slatkin et al. (2007)</u>: N (double-blind phase) = 86; 33 males; mean age = 53.9 (SD = 11.3) years; number of treated episodes = 223 for placebo and 493 for FBT; mean pain intensity at time 0 = 6.4 (SD = 1.7) for placebo and 6.4 (SD = 1.8) for FBT.</p>
<p>Interventions</p> <p>INFS v OTFC v FBT v IRM:</p> <p>First phase of each study consisted of an open-label dose titration phase to titrate each patient to successful dose before entry into double-blind phase for administration of a predetermined number of treatments containing either the intervention or placebo. FBT and OTFC patients were instructed to self-administer the entire dose within ca 15 mins.</p>
<p>Outcomes</p> <p>Pain intensity difference at 15, 30, 45 and 60 mins measured on an 11-point scale (0 [no pain] – 10 [as bad as you can imagine]). The authors suggest that a ≥ 2-point reduction in pain intensity difference is associated with meaningful pain relief.</p>
<p>Results <i>Only the results relevant to the present PICO are reported</i></p> <p>Bayesian fixed effects mixed-treatment comparison (network meta-analysis):</p> <p><u>Pain intensity difference</u>: INFS > IRM at 15 min (mean = 1.7, 95% credible interval (CrI) 1.1-2.3), 30 mins (mean = 1.4, 95% CrI 0.8-2.1), 45 mins (mean = 1.1, 95% CrI 0.5-1.7) and at 60 mins (mean = 0.9, CrI 0.2-1.6).</p>
<p>General comments</p> <p>No explicit search strategy included</p> <p>Data extraction checked by 2nd reviewer</p> <p>Cancer patients only</p>
<p>References of Included Studies (For systematic reviews):</p> <ul style="list-style-type: none"> - Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). <i>Douleurs</i> 2002;3(1): 26–35. - Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). <i>Pain</i> 2001;91(1-2): 123–30. - Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. <i>Journal of the National Cancer Institute</i> 1998;90(8): 611–16. - Kress HG, Oronska A, Kaczmarek, Z, et al. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microgram for breakthrough pain in patients with cancer: A phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. <i>Clin Therapeut</i> 2009; 6: 1177-91. - Mercadante S, Radbruch L, Davies AN, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain – and open-label, randomised, crossover trial. <i>Curr Med Res Opin</i> 2009; 25: 2805-15. - Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. <i>Pain</i> 1999;79(2-3):303–12. - Slatkin N, Xie F, Messina J, et al. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. <i>J Support Oncol</i> 2007; 7: 327-34.
<p>Citation: Zeppetella, Giovambattista and Ribeiro, Maria. Opioids for the management of breakthrough (episodic) pain in cancer patients. SO: Zeppetella Giovambattista, Ribeiro Maria DC. Opioids for the management of breakthrough (episodic) pain in cancer patients. Cochrane Database of Systematic Reviews: Reviews 2006 [1]. 2006. John Wiley & Sons, Ltd.</p>
<p>Design: Cochrane review w/o meta-analysis</p> <p>Country: United Kingdom</p> <p>Aim: To determine the efficacy of opioid analgesics given by any route, used for the management of breakthrough pain in patients with cancer, and to identify, and quantify, if data permit, any adverse effects of this treatment.</p>
<p>Inclusion criteria</p> <p>All RCTs, blinded and non-blinded, published and unpublished, which compare opioid analgesics with placebo/other opioid analgesics/both/other active controls, given in any dose and by any mode of administration for the relief of breakthrough pain, in patients of all ages in any setting who are treated with opioids for cancer pain.</p>
<p>Exclusion criteria</p> <p>None listed</p>

Population

4 RCTs were included: 3 of which were not relevant to the current question (2 compared starting doses of oral transmucosal fentanyl citrate (OTFC; Christie et al., 1998; Portenoy et al., 1999) and 1 compared oral transmucosal fentanyl citrate with placebo (Farrar et al., 1998)). The 4th RCT compared OTFC with immediate-release morphine (IRM; Coluzzi et al., 2001) and the results of this RCT are the only results that are reported from this Cochrane review.

Coluzzi et al. (2001):

- N = 134 adult cancer out-patients from 19 American university and community-based hospitals and clinics using an oral opioid equivalent to 60-100 mg oral morphine per day or 50-300 mcg/h of fentanyl-TTS who had identified a successful dose of normal release morphine to treat their target breakthrough pain for at least three consecutive days.
- 93 patients were titrated to a successful OTFC dose (The commonest reasons for not completing the titration were protocol violation (N = 17 participants), adverse events (N = 14; in N = 5 adverse events were OTFC-related)).
- 89 of these 93 randomised patients used at least one set of study medication
- 47 of these 89 patients were males, mean \pm SD age of all participants = 55 ± 11 years and the commonest cancers were lung (N = 15), breast (N = 14), and colorectal (N = 13). Participants around the clock opioids included morphine (N = 43), transdermal fentanyl (N = 28), oxycodone (N = 14), methadone (N = 3), and hydrocodone (N = 1). Participants were using a variety of rescue medication, the commonest of which were morphine (N = 66), oxycodone (N = 11), hydrocodone (N = 4), and hydromorphone (N = 3), and propoxyphene (N = 1). The pathophysiology of target breakthrough pains was somatic (N = 46), visceral (N = 25), neuropathic (N = 17), and unknown (N = 1).

Interventions**Coluzzi et al. (2001): OTFC v IRM:**

Phase one of the study was an open label OTFC titration to determine the dose that successfully treated the target breakthrough pain with acceptable adverse effects. Participants were commenced on 200 mcg of OTFC and if more than one unit was required to successfully manage the pain a larger unit was used for subsequent pains. Once a successful dose was found participants entered phase two when they were given 10 pre-numbered oral transmucosal units and capsules; 5 contained the successful dose of OTFC with placebo capsules and 5 contained placebo oral transmucosal lozenge and the participants' pre-trial successful dose of immediate-release morphine capsules.

Outcomes

Coluzzi et al. (2001): Pain intensity (measured by 11-point rating scale), pain relief and global satisfaction (both measured by 5-point rating scale)

Results**Coluzzi et al. (2001):**

- Jadad score 5/5; allocation concealment unclear.
- 75 patients treated at least one breakthrough pain with both OTFC and IRM (included in the primary efficacy analysis)
- 5 participants titrated to the 1600mcg dose without obtaining adequate relief.
- The mean \pm SD IRM and OTFC doses for the 93 participants enrolled to the double-blind phase of the study were 31 ± 13.5 mg and 811 ± 452 mcg, respectively.
- There was no relationship between the normal release morphine and OTFC doses ($R^2 = 0.065$) or between the successful dose of rescue medication (IRM or OTFC) and around the clock oral or transdermal opioids.
- In the primary efficacy analysis OTFC was significantly superior to IRM in terms of pain intensity difference ($p < 0.008$) and pain relief ($p < 0.009$) at 15, 30, 45 and 60 minutes, and global performance rating ($p < 0.001$). *Descriptive data presented in graph form in original paper [not extracted].*
- In addition, significantly ($p < 0.001$) more pain episodes treated with OTFC had a $> 33\%$ change in pain intensity at 15 minutes than IRM.
- The most frequent reported adverse effects in 134 participants were somnolence (N = 20), nausea (N = 18), constipation (N = 14), and dizziness (N = 10). All adverse effects occurred during either OTFC titration or during double blind phase, at which time participants were receiving around the clock opioids, OTFC and IRM and it is therefore difficult to attribute an adverse effect specifically to OTFC or IRM.
- N = 18 withdrew from the study due to adverse effects, 6 of which were considered at least partly due to study medication.
- Percentage of breakthrough pains requiring additional rescue medication: OTFC = IRM.

General comments

- Comprehensive search (incl handsearch and search for unpublished data)
- Independent screening of studies for inclusion/exclusion by 2 reviewers
- Cancer patients only
- Quality of included studies assessed using the Jadad score

References of Included Studies (For systematic reviews):

- Christie JM, Simmonds M, Patt R, Coluzzi P, Busch MA, Nordbrock E, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *Journal of Clinical Oncology* 1998;**16**(10):3238–45.
- Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Douleurs* 2002;**3**(1): 26–35.
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- Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *Journal of the National Cancer Institute* 1998;**90**(8): 611–16.
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3.9 Management of constipation

Review question 3: What is the most effective management of side effects of strong opioids?

3a: Is laxative treatment more effective with or without opioid switching in reducing constipation in patients with advanced and progressive disease who are taking strong opioids and experience constipation as a side effect?

No evidence was identified for this review question

3.10 Management of nausea

3b: Is anti-emetic treatment more effective with or without opioid switching in reducing nausea in patients with advanced and progressive disease who are taking strong opioids and experience nausea as a side effect?

No evidence was identified for this review question

3.11 Management of drowsiness

3c: Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect?

No evidence was identified for this review question

Opioids in palliative care:
safe and effective prescribing of strong
opioids for pain in palliative care of
adults

Appendix F – Full health economic report
May 2012

Developed for NICE by the National Collaborating Centre for Cancer
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Introduction

Patients with advanced and progressive disease for whom non-opioid analgesics and opioids conventionally used in the management of moderate pain have failed to control pain are indicated to receive strong opioids. However, there is uncertainty over the choice of strong opioids for the maintenance treatment of background pain.

The most commonly used therapy is oral sustained-release morphine, primarily because it is cheap and easy for the patients to take. However, recently, the use of transdermal opioids (fentanyl and buprenorphine) as a first-line approach to moderate to severe pain has increased substantially. Transdermal opioid therapies may be preferred over oral therapies because of better patient compliance, a better safety profile and the preference of the patient (Tassinari et al. 2008).

Aims

This economic evaluation aimed to assess the cost-effectiveness of first-line opioid maintenance treatments in patients with advanced and progressive disease who require strong opioids. The analysis considered the perspective of the National Health Service (NHS).

Method

Existing Economic Evidence

A systematic literature review was performed to assess the volume and quality of the current economic literature. Three relevant studies were identified; Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006). Each of these studies described the development of an economic model to assess the cost-effectiveness of oral opioids. Health effects were quantified in terms of quality adjusted life days (QALDs) and/or quality adjusted life years (QALYs). Table 1 shows the modified grade profiles for each of the three studies.

Table 1: Modified GRADE table

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Neighbors et al. 2001	Cancer and non-cancer patients with moderate to severe chronic pain	Fentanyl transdermal therapeutic system (A)	\$2,491	243.62 QALDs	Reference			One-way sensitivity analysis was performed on the key variables of interest (as identified by the authors).	Partially applicable	Potentially serious limitations
		Controlled release morphine (B)	\$2,037	235.63 QALDs	\$454	7.99 QALDs gained	\$20,709 / QALY gained	Range of cost-effectiveness results:		
		Controlled release oxycodone (C)	\$2,307	230.94 QALDs	\$184	12.68 QALDs gained	\$5,273 / QALY gained	A vs. B: an ICER of \$1,553 to A being dominated by B. A vs. C: A is dominant to an ICER of \$487,474		
	Comments: Considers a US perspective. Sponsored by manufacturer.									
Lehmann et al. 2002	Patients with non-malignant moderate to severe chronic pain.	Controlled release morphine	DM 6,186.48	216.16 QALDs	Reference			One-way sensitivity analysis was performed on the key variables (as identified by the authors). The ICER value varied from fentanyl being	Partially applicable	Potentially serious limitations

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		Transdermal fentanyl	DM 6,950.19	233.67 QALDs	DM 763.71	17.51 QALDs	DM 15,920 / QALY gained	dominant to a value of DM 40,738. The authors identified the price of fentanyl as a key driver of the analysis.		
Comments: Considers a German perspective. Sponsored by manufacturer.										
Greiner et al. 2006	Patients with non-malignant moderate to severe chronic pain.	Transdermal fentanyl (A)	€2,947.85	0.539 QALYs	Reference			Parameter uncertainty was assessed using probabilistic sensitivity analyses (PSA). Results were reported as robust to changes, with an ICER of €10,000 or less in 93% of runs. Additionally, one-way sensitivity analysis was carried out on the probability of skin irritation with Fentanyl TTS. However, the effect on the ICER was found to be minimal.	Partially applicable	Potentially serious limitations
		Sustained release morphine (B)	€2,883.44	0.499 QALYs	€64.41	0.04 QALYs	€4.45 / QALD gained €1,625.65 / QALY gained			
		Transdermal buprenorphine (C)	€3,151.13	0.537 QALYs	-€267.69	0.002 QALYs	A is dominant			
		Controlled release oxycodone (D)	€2,911.13	0.502 QALYs	€240.00	0.037 QALYs	€2.75 / QALD gained €1,003.03 / QALY gained			

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		Additional scenario: D vs B	NA	NA	€27.69	0.003 QALYs	€19.79 / QALD gained €7,224.62 / QALY gained			
	Comments: Considers a German perspective. Sponsored by manufacturer									

All the studies were based around the same model structure. Lehmann et al. (2002) and Greiner et al. (2006) used the same basic model structure employed in the study by Neighbors et al. (2001). Of the three papers, two considered a German perspective (Lehmann et al. 2002 and Greiner et al. 2006) while the remaining study considered a US perspective (Neighbors et al. 2001). Reflecting the growing use of opioids in patients with non-malignant diseases, two of the three studies consider non-cancer patient populations with the remaining study considering a cancer and non-cancer population.

All the studies found transdermal fentanyl to be cost-effective against oral sustained-release morphine with incremental cost-effectiveness ratios (ICERs) of £17,798, £14,487 and £1,406 per QALY in the studies by Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006), respectively. In addition, Greiner et al. (2006) showed transdermal buprenorphine to be cost-effective against oral sustained-release morphine with an ICER of £6,248 per QALY.

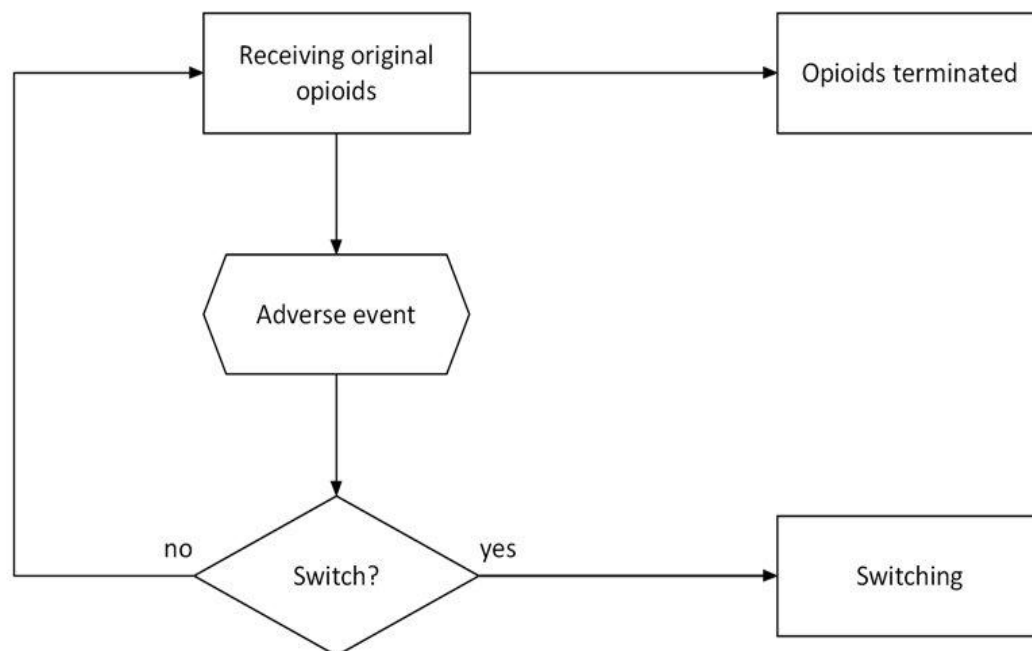
All three of the studies were deemed only partially applicable to the guideline. This was mostly a result of the studies considering countries other than the UK. In some instances, there were also concerns about the applicability of the quality of life data because they were often based on assumptions by a panel of clinical experts rather than reported directly from patients. Furthermore, potentially serious limitations were identified with all of the included studies. Many of the key model parameters, such as efficacy and resource use were estimated using the opinion of a panel of clinical experts. In addition, potential conflicts of interest were identified in all of the studies, as the analyses were sponsored by pharmaceutical companies.

De Novo Economic Model

Since the current economic literature didn't adequately address the decision problem, a de novo Markov model was developed to assess the cost-effectiveness of first-line strong opioid treatments. Markov models involve dividing a patients' possible prognosis into a series of discrete health states. In this case, the health states were "Receiving original opioids", "Opioids terminated" and "Switching." The structure of the economic model is shown in figure 1.

In comparison to previous models, the structure of this model is relatively simple. In general, when building economic models, there is a trade-off between complexity and transparency with more complicated models being more poorly understood. Thus, it is good practice for economic models to be no more complicated than necessary to answer the decision problem. In this instance, the simplicity of the model reflects the results of the clinical data review whereby adverse events were identified as the only significant difference between treatments (see "Clinical data" section for more details).

Figure 1: Structure of health economic model



Patients enter the model when commencing maintenance therapy and start in the "Receiving original opioids" health state. At each weekly cycle, patients may transition to the "Switching" health state, the "Opioids terminated" health state or remain in the "Receiving original opioids" health state. Movement between the states is determined via transition probabilities (see "Clinical data" section for more details). Patients move to the "Opioids terminated" health state following spontaneous, non-treatment related resolution of pain symptoms. Patients move to the "Switching" health state following treatment discontinuation due to the occurrence of an adverse event.

Note that the "Switching" and "Opioids terminated" health states are 'absorbing' health states meaning that patients cannot leave the state once they have entered it. Thus a spontaneous resolution of pain is assumed to last for the duration of the modelled time horizon. Likewise, patients who switch remain on their second therapy for the duration of the modelled time horizon (i.e. it is assumed that the second therapy will be effective and tolerated, thus patients can only switch once).

Each of the health states have an associated cost and benefit tariff that patients accrue while in that state. The costs reflect the therapy that the patient is currently receiving as well as the cost of any other resource use that may be required (e.g. community nurse visit). Patients in the "Receiving original opioids" state incur the cost of the opioids that they started with, while there is no cost for patients in the "Opioids terminated" state. Patients in the "Switching" health state will receive the cost of an alternative therapy (calculated as the average cost of the treatments under comparison). In addition, the transition to the switching state has a "one-off" cost associated with administering the new therapy and monitoring the patient.

In terms of benefits, each health state has an associated quality of life (QoL) tariff. This reflects the model's measurement of benefits in terms of QALYs, whereby the

quantity and quality of life can be expressed simultaneously. Patients in the “Receiving original opioids” and “Switching” health state will get a QoL value associated with controlled pain. Patients in the “Opioids terminated” health state will get a utility value associated with reduced pain. Utility decrements are also applied to reduce QoL in those patients that experience adverse events.

The overall costs and benefits for each treatment are then estimated on the basis of the total length of time individuals spend in each health state over the time horizon that has been modelled. The analysis considered a number of different time horizons with a maximum time horizon of 1 year. These relatively short time horizons reflect the prognosis of patients receiving palliative care, with most unlikely to live beyond 1 year. Given that the maximum modelled time horizon was 1 year, discount rates were not necessary and so were not considered.

The GDG expressed particular interest in a time horizon of 4 weeks since this was the time period over which they expected the therapies to differ most.

Clinical data

The results of the clinical review were used to inform the economic model. The review suggested that the proportion of patients experiencing pain relief could be higher with oral sustained-release morphine than with oral sustained-release oxycodone, transdermal fentanyl and transdermal buprenorphine (Bekkering et al. 2011). However, this was not the case in all patient populations or at all time points. Indeed, in the case of the comparison of oral sustained-release morphine with transdermal buprenorphine, the opposite was true (in patients with cancer pain or a treatment duration greater than 1 month, pain relief was lower with oral sustained-release morphine than with transdermal buprenorphine). Furthermore, the review showed that there were no statistically significant differences in the proportion of patients who discontinue as a result of a lack of efficacy. Thus, in the base-case analysis, it was assumed that all therapies were equally effective (in terms of pain relief).

The selection of the adverse events to be considered in the model was informed by the clinical evidence review. Side effect differences were reported for the comparison of oral sustained-release morphine and oral sustained-release oxycodone. According to Reid et al. (2006), oral sustained-release oxycodone was associated with a reduction in the occurrence of dry mouth. However, this aspect was not considered in the cost-effectiveness analysis as it's unlikely to have any meaningful impact on costs and benefits. Lauretti et al. (2003) reported fewer nausea events with oral sustained-release oxycodone but this was based on a very small study population (N = 22). Other studies in larger populations didn't show significant differences in nausea (four out of five studies showed no statistically significant differences in side effects).

Given that oral sustained-release morphine and oral sustained-release oxycodone were equivalent in effectiveness terms, it was decided that this comparison would not need to be modelled. A decision on the most cost-effective treatment option could instead be based on the therapy costs associated with each treatment.

Statistically significant reductions in constipation were observed in those patients receiving transdermal therapies compared with oral sustained-release morphine (Tassinari et al 2008). In addition, patients receiving transdermal buprenorphine had significantly fewer gastrointestinal side effects than patients receiving oral sustained-release morphine. However, the comparison of oral

sustained-release morphine and transdermal buprenorphine was based on a study with low patient numbers (N=52) and was judged to be of very low quality.

Given the limitations of the evidence base for oral sustained-release morphine and transdermal buprenorphine, it was decided that this comparison would not be considered in the economic evaluation.

Thus, only the comparison of transdermal fentanyl and oral sustained-release morphine were considered in the economic model. Table 2 shows the weekly adverse event occurrence and discontinuation probabilities that were applied in the model for each treatment.

Table 2: Adverse event occurrence and discontinuation

Adverse event	Adverse event occurrence		Discontinuation following adverse event
	Morphine	Fentanyl	
Constipation	12.26%	6.24%	4.06%

Since there was a lack of reliable evidence describing discontinuations resulting from individual adverse events, discontinuations as a result of constipation were estimated using data from the Bekkering study. The weighted average weekly discontinuation rate due to adverse events was calculated for each therapy. Differences in discontinuations by therapy were assumed to be attributed to the differences in the occurrence of constipation by therapy (under the rationale that there were no significant differences in other adverse events).

Following the advice of the GDG, discontinuations following adverse events were assumed to only occur in the first 4 weeks of treatment. This reflects the experiences of the GDG in clinical practice whereby discontinuations in the first 4 weeks are driven by safety concerns while discontinuations thereafter are driven by a lack of adequate pain relief (not considered in the model since treatments are assumed to be equal in terms of pain relief).

In the absence of data, the GDG estimated that there would be a spontaneous, non-treatment related, resolution of pain in 5% of patients in the 1-year period. Thus, the model assumes that 0.10% of patients would transition to the "Opioids terminated" at each weekly cycle.

Mortality was not considered in the economic model. This decision was made because of the difficulty of sourcing mortality data appropriate for the population under consideration. A suitable mortality rate would have to reflect the wide range of possible disease areas that may cause a patient to require strong opioids and this was considered to be unfeasible. Thus, an alternative approach was adopted in the model whereby different time horizons were used to reflect a patient that lives for 1 month, 2 months, 3 months, 6 months and 12 months.

Cost data

The unit costs of the drugs considered in the model were sourced from the British National Formulary (BNF 61). Table 3 shows the doses and weekly therapy costs of the interventions of interest in the economic evaluation.

Table 3: Therapy costs and doses

Therapy	Dose	Unit	Average weekly cost (£)
Morphine*	60	mg/day	2.33
Oxycodone^	30	mg/day	10.49
Fentanyl†	25	µg/hour	11.84
Buprenorphine‡	35	µg/hour	6.88

*Morphgesic® SR, MST Continus® and Zomorph®

^OxyNorm® and OxyContin®

†Fentanyl (non-proprietary) and Durogesic DTrans®

‡Transtec®

The 60mg starting dose of oral sustained-release morphine was sourced from a published study by Brooks et al. (1995) who conducted a regional survey of opioid use by patients receiving specialist palliative care. This dose is in accordance with the BNF's recommendation that a starting maintenance dose of 20-30mg should be given every 12 hours. The equivalent dose of oral sustained-release oxycodone, transdermal fentanyl and transdermal buprenorphine were calculated using a dose equivalence table from the BNF combined with advice from the GDG.

Note that since the model starts when patients commence maintenance therapy, the costs incurred when titrating to an effective dose are not considered. Furthermore, the average doses applied in the above table are assumed to be effective for the duration of the modelled time horizon. Thus, dose increases are not considered in the model.

To reflect clinical practice, patients were assumed to receive laxatives concomitantly for the prevention of constipation. Based on the advice of the GDG, patients receive an average cost of the laxatives that are typically given to patients receiving opioids. Average costs were calculated using cost and dose information from the BNF and are shown in table 4.

Table 4: Concomitant laxatives for the prevention of constipation

Therapy	Medications and doses	Average weekly cost (£)
Co-danthramer	Non-proprietary: 25/200 [†] capsules; 1-2 times daily, 37.5/500 [†] strong capsules; 1-2 times daily, 25/200 ^{†*} suspension; 5ml and 10ml daily, 75/1000 ^{†*} strong suspension;; 5ml daily	2.61
Co-danthrusate	Non-proprietary: 50/60 [‡] capsules; 1-3 daily, 50/60 ^{‡^} suspension, 5-15ml daily	3.29
Lactulose solution	Non-proprietary: solution 15ml twice daily	1.28
Senna	Non-proprietary: 7.5mg tablets; 2-4 daily, Senokot: syrup 7.5mg^ 10-20ml daily	0.54
Movicol	Oral powder: macrogol '3350' sachet~; 1-3 daily	3.12
Laxido	Oral powder: macrogol '3350' sachet~; 1-3 daily	3.12
Dulcolax	Perles® (=capsules); 5-10mg daily	1.59
Magnesium hydroxide	Non-proprietary: 20ml twice daily	1.26
Overall		2.10

Therapy	Medications and doses	Average weekly cost (£)
†	Dantron to poloxamer ratio, e.g. 25/200 = dantron 25 mg, poloxamer '188' 200 mg	
‡	Dantron to docusate sodium ratio, e.g. 50/60 = dantron 50 mg, docusate sodium 60 mg	
*	Dose per 5ml	
^	Dose per ml	
~	13.125g sodium bicarbonate, 178.5mg sodium chloride, 350.7mg potassium chloride, 46.6mg per sachet	

Despite receiving concomitant laxatives to prevent constipation, patients in the model may still experience a constipation "event" (see the occurrence probabilities in table 1). Only the medication costs associated with a constipation event were considered in the model. It was assumed that patients will regularly make visits to the GP while receiving opioid therapy and additional visits would not be made in response to an adverse event.

The GDG advised that in the occurrence of a constipation event, patients would most likely receive strong oral laxatives or suppositories. However, in some 10% of patients (estimated by the GDG) an enema would be required. Table 5 shows the estimated cost of a constipation event that was applied in the model (using unit cost and dose information from the BNF).

Table 5: Constipation event costs

Therapy	Resource use	Average weekly cost (£)
Senna and docusate	Non-proprietary: 7.5mg tablets; 2-4 daily, Senokot: 7.5mg† syrup l 10-20ml daily	4.86
Bisacodyl suppositories	Non-proprietary: suppositories 10-20mg daily	0.97
Glycerol suppositories	Glycerin: suppositories 4g‡ daily	0.86
Enema		
Drug costs	Norgalax Micro-enema® 10-g* unit, Relaxit Micro-enema® 5ml^, Micralax Micro-enema® 5ml~, Micolette Micro-enema® 5-10ml§	0.48
Administration cost	20 minute home visit by community nurse≈	24.00
Patients requiring enema		10%∞
Overall		4.68

† Dose per 5ml

‡ Gelatin 140 mg, glycerol 700 mg, purified water to 1 g

* Docusate sodium 120mg in 10-g dose

^ Sodium citrate 450 mg, sodium lauryl sulphate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose

~Sodium citrate 450 mg, sodium alkylsulphoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose

§Sodium citrate 450 mg, sodium lauryl sulphoacetate 45 mg, glycerol 625 mg, together with potassium sorbate and sorbitol in a viscous solution, in 5-mL

≈Average length of 20 minutes from PSSRU (Netten and Curtis)

∞Assumption made by guideline development group (GDG)

Patients moving into the "Switching" health state receive a one-off cost associated with the process of switching. As shown in the table 6, this cost encompassed the cost of a GP visit, advice from a medical consultant (sought by GP), community nurse visit and GP telephone consultation.

Table 6: 'One-off' switching cost

Resource	Duration (minutes)	Cost (£)
GP surgery visit	11.7*	32.00
Medical consultant	10†	24.33
Community nurse visit	20.0*	24.00
GP telephone consultation	7.1*	19.00
Total	-	99.33

* Based on the average length of consultation reported in Netten and Curtis

†Assumption

It is assumed that patients in the "Switching" health state would receive one of the treatments under consideration (oral sustained-release morphine, oral sustained-release oxycodone, transdermal fentanyl or transdermal buprenorphine) that they have not received. In the model this is estimated as the average cost of the three treatments that the patient has not received. For example, patients switching from oral sustained-release morphine would receive an average of the cost of oral sustained-release oxycodone, transdermal fentanyl and transdermal buprenorphine.

This assumption was necessarily made because of a lack of data on the treatments that patients receive following a discontinuation of treatment with oral sustained-release morphine or transdermal fentanyl. For simplicity, the treatments that patients could receive were restricted to the therapies under consideration. In reality, there is a wide range of potential treatments that the patients may receive (including non-opioid treatments). The impact of varying the treatment to which patients will switch is assessed in the sensitivity analysis.

The switching costs for patients switching from oral sustained-release morphine and transdermal fentanyl are shown in table 7.

Table 7: Switching costs

Switching from	Switching to	Average weekly cost
Morphine	Oxycodone, fentanyl or buprenorphine	£9.58
Fentanyl	Morphine, oxycodone or buprenorphine	£6.43

Health-related quality of life data

All patients receive a baseline quality of life of 0.592, which is associated with controlled pain. This value was based on a study by Goosens et al. (1999) in patients with chronic low back pain where a standard gamble technique was used to elicit the utility values. In the absence of suitably high quality data in the direct population of interest, this value was assumed to be representative of patients requiring strong opioids. This value was also used in the cost-effectiveness analysis by Greiner et al. (2006).

Patients who experience a constipation event incur a utility decrement of 0.072. This value was derived from SF-36 data from a systematic review of constipation on quality of life in adults and children (Belsey et al. 2010). Since NICE typically expresses a preference for the EQ-5D classification system when measuring quality

of life (see NICE's ['Guide to the methods of technology appraisal'](#)), a published mapping equation (Ara et al. 2008) was used to convert the SF-36 data to EQ-5D data. This particular mapping equation was chosen because it performed effectively in the validation exercise carried out by the authors (whereby mean statistics from published studies were used to validate the results).

Sensitivity analysis

To estimate uncertainty and determine the key drivers of the model, a series of one-way sensitivity analyses were conducted. One-way sensitivity analysis involves changing one input parameter, re-running the model and recording the new cost-effectiveness result. Analyses were conducted where the value of an input variable was uncertain and the influence of changes to this variable on the cost-effectiveness result could be substantial.

Since the main benefit of transdermal fentanyl over oral sustained-release morphine is the reduction in constipation, changes to constipation-related variables could have a considerable influence on the cost-effectiveness result. Thus, changes to the discontinuation rate following constipation, the disutility associated with constipation and the proportion of patients requiring an enema following constipation were considered. In the absence of alternative evidence on the discontinuation associated with constipation, the discontinuation rate was increased to 50% and 100%. An alternative constipation utility decrement of 0.20 was sourced from a study by Penning Van Beest et al. (2010). Given the lack of evidence on the proportion of patients requiring an enema, alternative values of 50% and 100% were assumed.

Differences in constipation between the two treatments also manifest themselves in differences in the number of patients that switch. Therefore, changes to the cost of switching (i.e. the switching event) and the weekly cost associated with the "Switching" health state could have a considerable impact on the cost-effectiveness result. In the absence of alternative evidence on the switching cost, a scenario where the base case switching cost was doubled was considered. Changes were made to the weekly cost associated with the "Switching" health state by changing the assumption about the treatment that patients receive following a switch. Scenarios were considered whereby patients switch to buprenorphine, oxycodone or the direct comparator (e.g. if discontinuing oral sustained-release morphine, then switch to transdermal fentanyl).

An area of concern for the GDG was the potential for higher average maintenance doses than those assumed in the base case. Thus, based on a study by Lundorff et al. (2007), an oral sustained-release morphine dose of 120mg/day and transdermal fentanyl dose of 50µg/hour were considered.

To further estimate uncertainty in the model, probabilistic sensitivity analysis (PSA) was performed. PSA involves running a series of simulations where the values of the model's input parameters are randomly sampled from a distribution around their mean value (informed, where possible, by some measure of variance reported in the relevant study). This analysis is useful for assessing the uncertainty around all parameter values simultaneously.

Table 8 shows the input parameters that were included in the PSA along with the standard deviations (SD) that were used to model the distribution. Note that it was assumed that cost inputs follow a gamma distribution while other input parameters were normally distributed.

Table 8: Parameters and distribution values for the PSA

Parameter	Mean	SD
Constipation occurrence: Morphine	12.26%	7.92%*
Constipation occurrence: Fentanyl	6.24%	3.96%*
Constipation utility decrement	0.072	0.018†
Constipation cost	£4.68	£2.34‡
Switching cost	£99.33	£49.67‡
Therapy costs: Morphine	£2.33	£1.17‡
Therapy costs: Fentanyl	£11.84	£5.92‡

* Estimated using data from the systematic review and meta-analysis by Bekkering et al. (2011).**Error! Bookmark not defined.**

† Estimated by applying alternative mapping equations**Error! Bookmark not defined.** to the SF-36 data reported by Belsey et al. (2010)**Error! Bookmark not defined.**

‡ SDs could not be sourced, so these values were assumed to be equal to 50% of the mean value

Results

The results of the economic model are presented as expected costs and QALYs for each treatment arm along with an incremental cost-effectiveness ratio (ICER) for each treatment comparison. The ICER is used to measure the cost-effectiveness of one treatment over another; it is calculated as shown in figure 2.

Figure 2: Calculation of the incremental cost-effectiveness ratio (ICER)

$$\text{ICER} = (\Delta \text{Cost}) / (\Delta \text{QALYs})$$

$$\text{ICER} = (\text{Cost Intervention A} - \text{Cost Intervention B}) / (\text{QALYs Intervention A} - \text{QALYs Intervention B})$$

It can be seen that by dividing the difference in costs of each treatment by the difference in benefits (in QALY terms), a cost per QALY can be calculated for each comparison. NICE typically adopts a threshold of £20,000 for one additional QALY gained. Thus, an intervention with ICER < £20,000 can usually be considered cost-effective. Interventions with ICER values above £30,000 are not typically considered cost-effective. For ICER values between £20,000 and £30,000, an intervention may be considered cost-effective if it is associated with significant benefits.

To aid understanding of the economic modelling results by all interested parties, the results are presented with the most expensive treatment as the reference case (i.e. intervention A in the above calculation).

Base case results

The base case results of the model are presented in table 9 for the comparison of transdermal fentanyl versus oral sustained-release morphine.

Table 9: Base case total expected costs, QALYs and ICERs for transdermal fentanyl versus oral SR morphine

Time point	Fentanyl		Morphine		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
1 month	£90	0.0452	£54	0.0449	£35	0.0003	£107,532

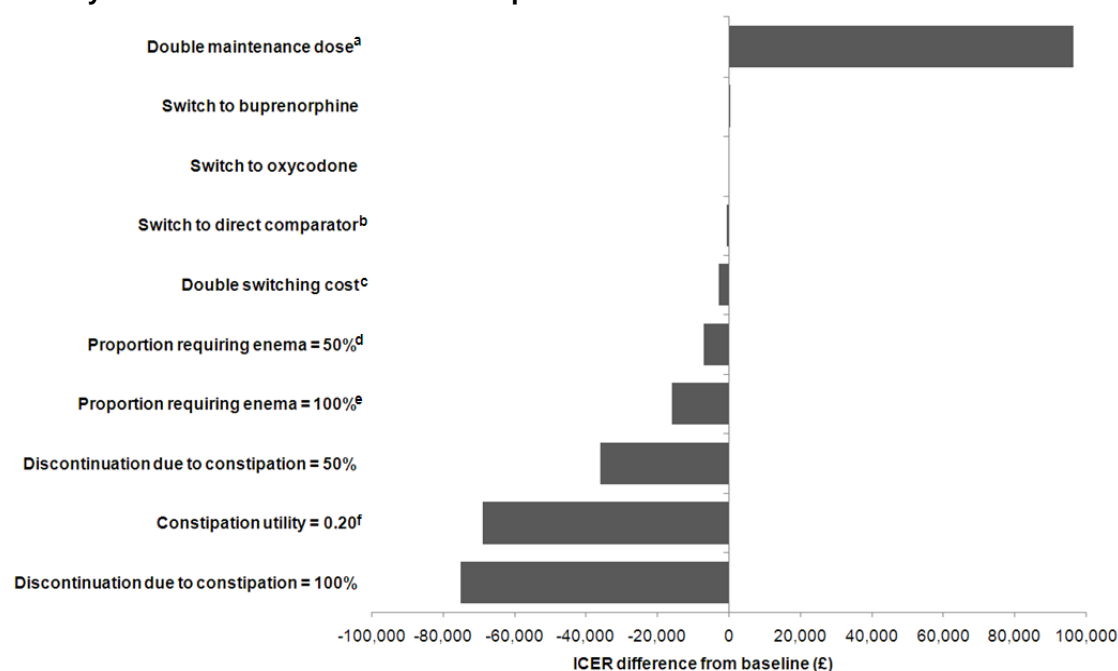
2 months	£178	0.0906	£107	0.0899	£71	0.0007	£109,469
3 months	£288	0.1474	£172	0.1463	£116	0.0011	£110,096
6 months	£573	0.2957	£342	0.2936	£231	0.0021	£110,268
12 months	£1,135	0.5950	£678	0.5908	£457	0.0042	£109,636

It can be seen that, at all time points, transdermal fentanyl provides an additional QALY benefit over oral sustained-release morphine but this comes at an additional cost. It can also be seen that the ICER result remains above £30,000 per QALY at all time points.

Sensitivity analysis

The results of the one-way sensitivity analyses are shown in figure 2 for the comparison of oral sustained-release morphine versus transdermal fentanyl. The x axis shows the difference in ICER value compared to the base case ICER with the vertical line representing the base case ICER result. Values to the left of the vertical line show that the ICER is lower than in the base case (i.e. more cost-effective) and values to the right of the vertical line show that the ICER is higher than in the base case (i.e. less cost-effective).

Figure 3: Results of one-way sensitivity analysis for the comparison of transdermal fentanyl and oral sustained-release morphine



^a Morphine dose of 120mg/day and fentanyl dose of 50µg/hour, based on [Lundorff et al. \(2007\)](#) and dose equivalence rates from the BNF.

^b Patients originally receiving morphine switch to fentanyl and patients originally receiving fentanyl switch to morphine

^c Increases switching cost to £198.66

^d Increases constipation event cost to £14.47

^e Increases constipation event cost to £26.71

^f Sourced from Penning van beest et al. (2010)

The results show that the model is sensitive to changes in the discontinuation rate associated with constipation, the utility decrement assigned to constipation and the average maintenance dose that is applied in the model. The increase in the dose required for effective maintenance increases the ICER value. Conversely, the changes to the discontinuation probability or utility associated with constipation have the effect of decreasing the ICER. However note that in all cases, the ICER value remains above £30,000 per QALY.

At the request of the GDG, threshold analysis was performed around the cost of switching. This was considered because of uncertainty around the amount of healthcare resources that would be utilised when patients switch. For example, there is potential for higher switching costs if the amount of specialist advice required for a switch increases. Threshold analysis finds the value of an input that is required for the ICER value to be below a cost-effectiveness threshold of £20,000 per QALY.

Threshold analysis revealed that a switching cost of £3,086 would be required for transdermal fentanyl to be cost-effective against oral sustained-release morphine at a threshold of £20,000 per QALY. Further analysis showed that when applying a utility decrement of 0.20 for constipation events (Penning et al. 2008), a switching cost of £1,873 and would be required for transdermal fentanyl to be cost-effective against oral sustained-release morphine at a threshold of £20,000 per QALY.

The results of the PSA are shown in figure 4 and figure 5, which depict the results using a cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC), respectively.

Figure 4: Probabilistic sensitivity analysis (PSA) results shown on a cost-effectiveness plane

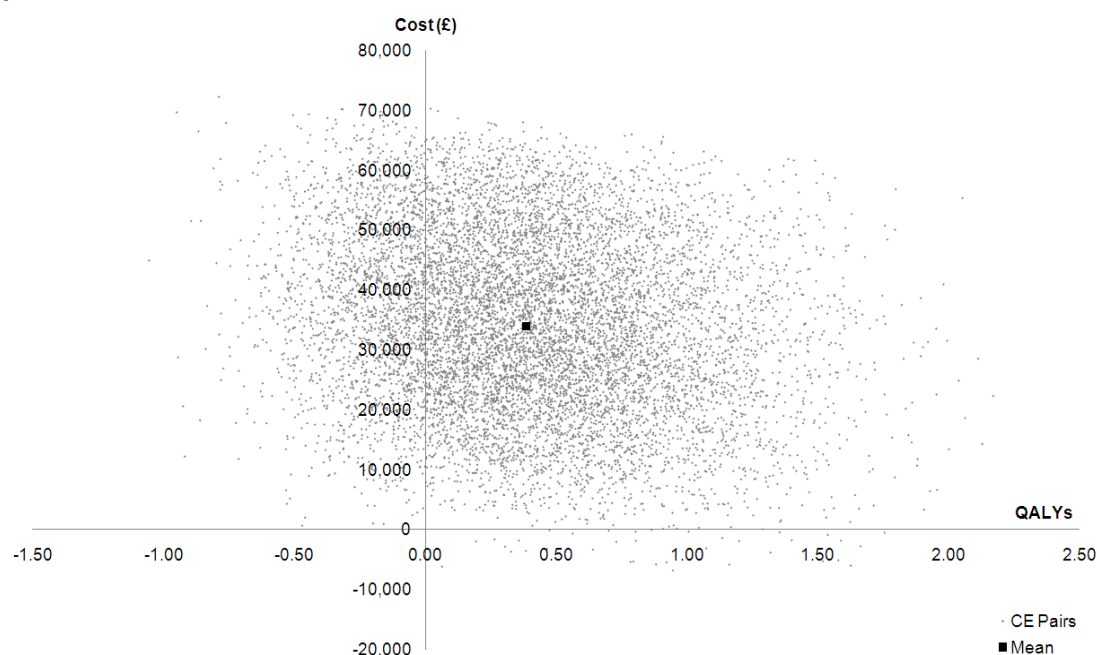


Figure 5: Probabilistic sensitivity analysis (PSA) results depicted using a cost-effectiveness acceptability curve (CEAC)

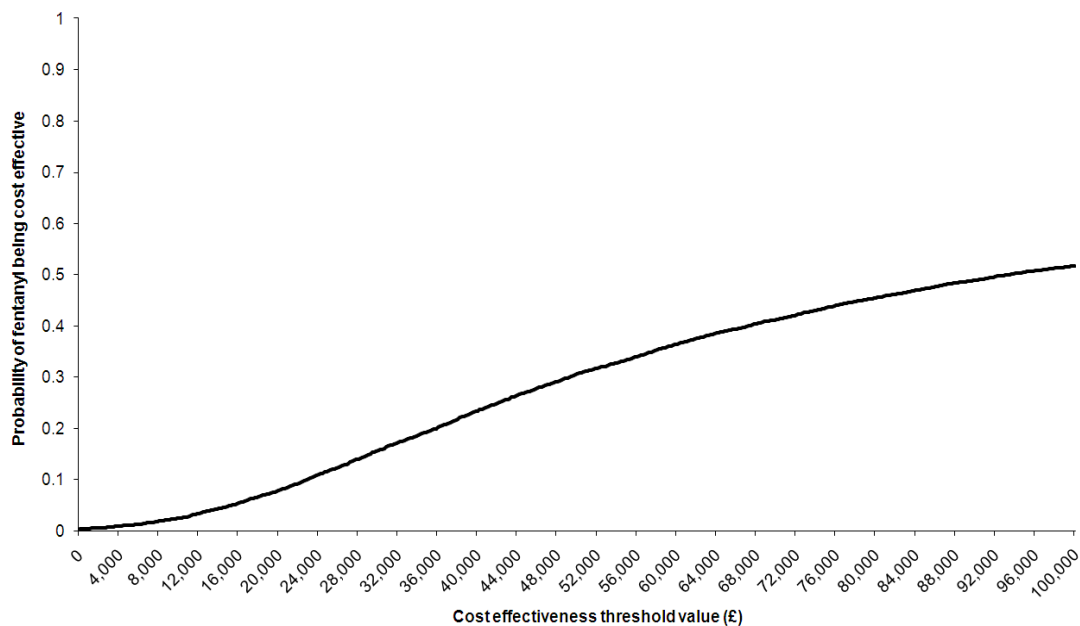


Figure 4 shows 10,000 cost-effectiveness pairs with each pair representing the result of an individual simulation in the PSA. The mean result based on these cost-effectiveness pairs is also shown. It can be seen that the mean result lies in the North East (NE) quadrant of the graph reflecting that fentanyl is more costly and more effective. It can also be seen that the majority of the cost-effectiveness pairs lie within the NE quadrant. However, note that the cost-effectiveness pairs are not tightly grouped around the mean value. Indeed, they are quite widely dispersed and span three of the four quadrants of the cost-effectiveness plane (NE, SE and NW). This suggests that there is considerable uncertainty around the mean result and that in some cases it's possible for transdermal fentanyl to be dominated or dominant in comparison to oral sustained-release morphine.

Figure 5 shows the probability that fentanyl is cost-effective against morphine at various cost-effectiveness thresholds. Thus, it gives a useful insight into how the uncertainty shown in figure 4 affects the cost-effectiveness decision. It can be seen from figure 5 that the probability of transdermal fentanyl being cost-effective increases as the cost-effectiveness threshold increases. At a cost-effectiveness threshold of £20,000 per QALY, it can be seen that the probability of transdermal fentanyl being cost-effective against oral sustained-release morphine is 8%.

Discussion

This analysis aimed to estimate the cost-effectiveness of strong opioids in patients with advanced and progressive disease for whom previous treatments have failed. The systematic review identified that there were few relevant studies conducted in this area. Furthermore, those studies that were identified had serious limitations and were considered only partially applicable to the guideline. Thus, a new economic evaluation was conducted.

The clinical evidence review showed that oral sustained-release oxycodone and oral sustained-release morphine were equal in effectiveness terms (nine out of nine studies showed no statistically significant differences in pain relief and four out of five studies showed no statistically significant differences in side effects). Thus, economic

modelling was not required for this comparison and a decision on cost-effectiveness could be made purely on the basis of the cost of treatment. Thus, since oral sustained-release morphine is cheaper than oral sustained-release oxycodone, oral sustained-release morphine is the more cost-effective treatment option (i.e. provides the same benefit but at a lower cost).

The clinical review for oral sustained-release morphine versus transdermal buprenorphine did not identify any studies that were of a high enough quality to be used as the basis for an economic model.

The clinical review for oral sustained-release morphine versus transdermal fentanyl did identify significant differences in effectiveness between the studies. Thus, economic modelling was conducted for this comparison. The base case results of the model suggest that, at a cost-effectiveness threshold of £20,000 per QALY, transdermal fentanyl is not cost-effective against oral sustained-release morphine at all time points.

The one-way sensitivity analysis that was conducted showed that the model was sensitive to changes in the average maintenance dose, the utility decrement associated with constipation and the probability of discontinuation following a constipation event. However, the ICER result in all analyses remained above £30,000 and so oral sustained-release morphine remained the more cost-effective treatment in all the analyses considered.

Threshold analysis was conducted on the switching cost required to attain cost-effectiveness at a threshold of £20,000 per QALY. The results showed that switching costs of £3,086 and £1,873 would be required when considering the base case scenario and the scenario with an increased utility decrement (0.20), respectively. These were considerably higher than even the highest switching costs expected by the GDG members.

The PSA showed considerable variation around the mean result. However, at a threshold of £20,000 per QALY there was only a 14% probability that transdermal fentanyl would be cost-effective against oral sustained-release morphine.

There are a number of limitations with the economic analysis that should be acknowledged. Firstly, the dose of strong opioids required for the effective management of pain typically increases over time. In the model, an average maintenance dose was applied for the duration of the modelled time horizon. However, the clinical evidence review didn't reveal differences in the amount of dose increases required for each treatment. Thus, given the differences in treatment costs, this assumption would most likely bias against oral sustained-release morphine. Therefore, if dose increases were to be considered in the model it would most likely only strengthen the conclusion that oral sustained-release morphine is the more cost-effective treatment.

A second limitation is the assumption that patients can only switch once. This implicitly implies that the second treatment that a patient receives is effective and well tolerated. The likely influence of this assumption on the cost-effectiveness result is somewhat difficult to ascertain. However, it is possible that allowing for multiple switches would improve the cost-effectiveness of transdermal fentanyl.

Conclusion

The results of the base-case analysis show that, in comparison with oral sustained-release morphine, transdermal fentanyl provides additional quality of life benefits to patients as a result of a reduction in adverse events. However, these benefits come at an additional cost and it was found that these benefits were not substantial enough to make transdermal fentanyl cost-effective in comparison to oral sustained-release morphine.

Oral sustained-release morphine holds a cost advantage over oral sustained-release oxycodone and transdermal buprenorphine. The clinical evidence shows that oral sustained-release morphine is equivalent to oral sustained-release oxycodone in effectiveness terms. Thus, in the average patient, oral sustained-release morphine provides the same benefit as oral sustained-release oxycodone but at a lower price. It can therefore be considered the more cost-effective treatment. The clinical evidence base for the comparison of oral sustained-release morphine and transdermal buprenorphine was considered to be of very low quality. It was therefore considered inappropriate to use it as the basis for an economic evaluation.

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